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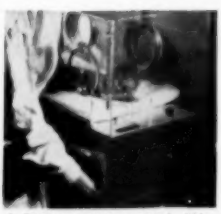

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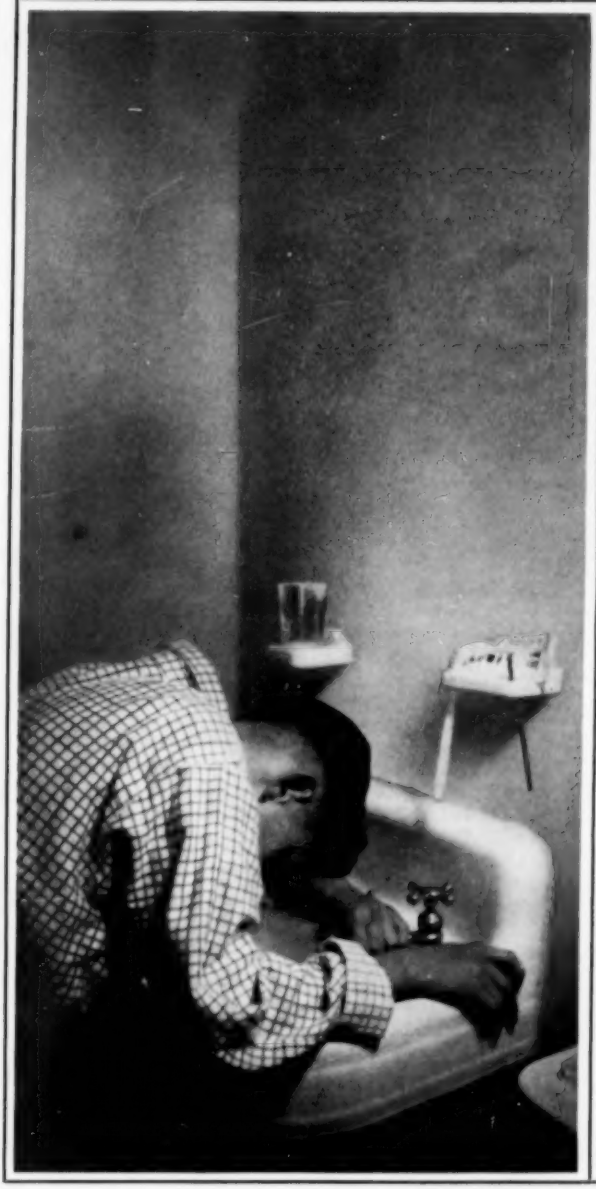

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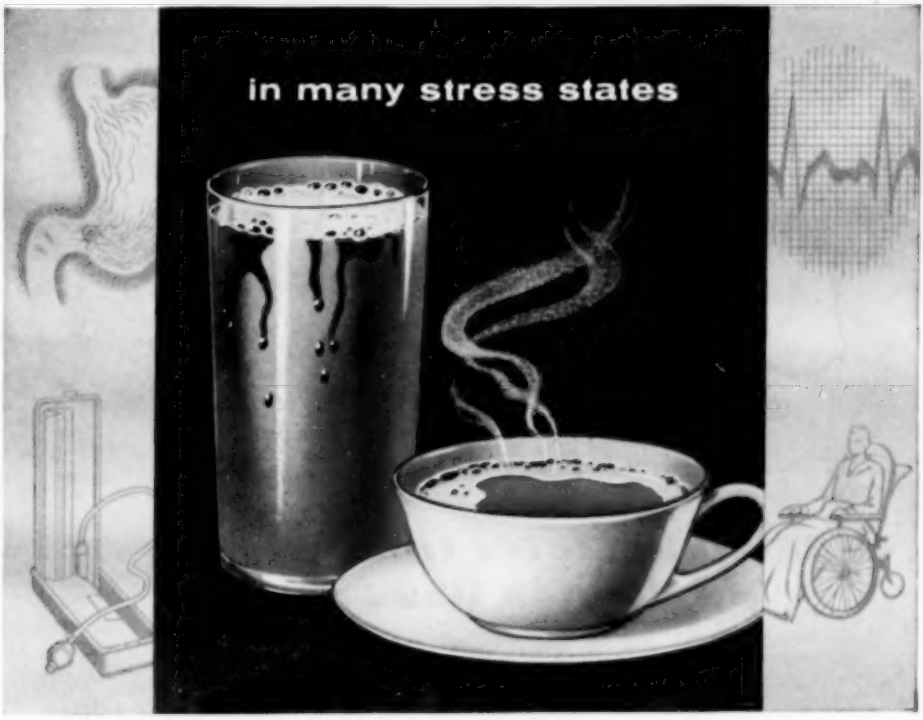

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Corticotropin (ACTH) Therapy of Nephrotic Syndrome in Children

I. Clinical Results and Effects on Proteinuria in One Hundred Six Instances

F. M. MATEER, M.D.; F. A. WEIGAND, M.D.; LAWRENCE GREENMAN, M.D.†; C. J. WEBER Jr., M.D.†; G. A. KUNKEL, M.D., and T. S. DANOWSKI, M.D., Pittsburgh

Intially corticotropin (ACTH) and cortisone were used only to induce diuresis in children with the nephrotic syndrome, though occasional remissions were produced.[1-7] Most of these early trials were of short duration and the amounts of drugs administered were small because of limited supplies and the occurrence of side-effects such as edema, hypertension, and hypokalemia. The demonstration that such changes could be prevented or minimized by means of diets rigidly restricted in sodium and high in potassium[8] enabled us and others[9,10] to undertake more prolonged administration of large amounts of corticotropin and adrenocortical steroids in the hope of influencing the course of the underlying disease.

Materials and Methods

During the past five years we have treated a total of 106 instances of nephrotic syndrome in children. All had persistent and usually massive proteinuria on admission. Each patient was treated in essentially the same way, and no attempt was made to exclude those with hypertension, formed elements in the urine, or azotemia. Data on 30 of these children have been reported earlier.[8] Seventy-two were initial attacks; the remainder represented exacerbations. From the information in Tables 1A and 1B it can be calculated that the mean age at which the initial episode of nephrotic syndrome occurred in the group of 72 children was 4 years 4 months, with 1½ to 2½ years the commonest age of onset and a range of 4 months to 13 years 7 months in the remainder. There were more boys than girls, 45 versus 27, and the latter were somewhat older at the first manifestation (4 years 9 months versus 4 years 2 months). Symptoms or signs of nephrotic syndrome, or both, had been present for one week to four years prior to hospitalization for the first course of corticotropin, with a mean duration of 27 weeks. This interval was much shorter, averaging four weeks, in patients who developed an exacerbation while under observation in the dispensary. A history of an infection prior to or coincident with the first episode of nephrotic syndrome was obtained in 40 of the 72 patients, with upper respiratory infection in 34, unexplained fever in 3, varicella in 2, and rubeola in 1 (Table 1A). In the 18 patients admitted one to six times with a total of 34 exacerbations, recrudescence followed an upper respiratory infection in 12 instances, bronchitis in 1 and was unassociated with any recognized infection in the remaining 21 (Table 1B). Beta-hemolytic streptococci were isolated from nose and throat cultures in only a minority of the initial and the subsequent attacks, 12% and 6%, respectively.

Submitted for publication Jan. 18, 1957; accepted Feb. 18.

From the University of Pittsburgh School of Medicine and the Children's Hospital of Pittsburgh. Established Investigator of the American Heart Association (Dr. Mateer).

Aided by grants from the Western Pennsylvania Heart Association, the American Medical Association and the American Cancer Society (Allegheny County Chapter and the M. O. Freas Estate).

† Dr. Greenman died June 20, 1956; Dr. Weber died Dec. 24, 1956.

TABLE 1A.—*Clinical Findings in Fifty-Four Initial Episodes of Nephrotic Syndrome*

Patient	Age, Yr.	Sex	Onset Date (Mo./Yr.)	Duration of Symptoms, Wk.	Antecedent Infection	Edema	Blood Pressure Before Rx	Albumin (0-4+)	RBC, No./HPF	Casts, No./HPF	Last Seen (Mo./Yr.)
‡1	7.1	M	10/55	12	0	+	108/54	4-4	0	2-26	2/56
*†2	3.1	F	12/52	2.5	URI	+	100/50	4-4	0	3-4	8/56
†‡3	6.9	F	7/55	12	0	0	90/32	0-4	1-2	0	3/56
4	2.7	M	12/54	4	0	+	104/68	4-4	0	Rare	2/56
*‡5	3.9	M	12/51	52	Pharyn.	+	100/60	4-4	2-15	1-3	3/56
6	2.4	M	1/56	4	0	+	88/48	4-4	25-125	0	8/56
*†‡7	7.7	M	4/51	20	0	+	118/78	2-4	1-3	3-4	6/56
‡8	2.6	M	10/53	4	0	+	96/62	4-4	0	Rare	2/55
‡9	2.6	F	6/54	12	URI	+	80/48	4-4	1-3	1-20	5/56
*‡10	2.5	M	11/53	13	0	+	100/60	4-4	7-8	Rare	8/56
*11	5.8	M	9/52	13	Pharyn.	+	90/50	4-4	0	Rare	3/56
‡12	2	M	5/52	10	URI	+	90/60	4-4	2	3-4	9/53
‡13	1.2	F	1/55	40	Fever	+	100/60	0-4	2-15	10-20	8/56
*‡14	5.0	M	6/51	156	Otitis	+	110/70	4-4	4-150	1-3	2/56
‡15	3.6	M	2/54	68	Fever	+	100/64	0-4	0	2	8/56
*‡16	3.4	M	11/51	17	URI	+	100/46	2-3	0	0	5/56
*‡17	2.5	F	7/54	13	URI	+	100/50	3-4	3-5	1-4	7/56
‡18	8.9	M	2/55	14	URI	+	110/72	4-4	0	Rare	6/56
19	9.0	F	10/52	7	Pharyn.	+	90/50	2-4	0	1-10	6/56
20	3.5	M	11/55	52	URI	+	90/56	4-4	0	6	1/56
*21	0.5	F	9/47	6	0	+	120/80	3-4	4-30	3-4	Died
‡22	1.7	M	5/55	5	0	+	120/40	1-4	0	0	3/56
*23	1.6	M	3/55	4	URI	+	88/48	4-4	Rare	1-4	7/56
‡24	4.1	F	10/53	32	Fever	+	90/40	0-4	0	Rare	8/54
‡25	5.0	F	3/51	208	Pharyn.	+	102/70	4-4	0	Rare	6/56
‡26	5.9	F	5/54	40	URI	+	96/60	0-4	0	Rare	1/56
*‡27	5.2	M	5/52	6	URI	+	100/60	4-4	2-4	3-5	5/53
*‡28	2.0	F	3/50	84	URI	0	90/50	0-4	0	0	3/56
*29	3.8	M	2/50	56	URI	+	108/62	0-4	1-10	Rare	6/56
30	4.1	M	5/51	4	0	+	102/72	2-4	2-3	2-3	6/56
31	1.7	M	12/54	10	0	+	100/50	4-4	Rare	0	7/55
32	1.0	M	12/53	10	Varicella	+	120/76	2-4	1-50	Loaded	7/56
33	2.4	M	11/53	4	URI	0	110/80	4-4	0	0	8/56
34	6.3	M	1/55	5	0	+	104/70	4-4	0	0	6/56
*‡35	7.6	F	2/45	20	URI	0	110/70	1-4	28-300	0	8/56
*‡36	7.0	F	7/52	36	0	+	91/42	Tr.-4	2-30	0	6/56
37	2.1	F	12/54	4	URI	+	—	4-4	0	Rare	6/56
38	1.6	M	4/54	4	0	+	124/82	4-4	10-100	Rare	Died
*39	13.6	M	12/50	52	0	+	110/70	4-4	Rare	2-3	1/56
*‡40	4.0	M	12/51	50	0	+	90/60	4-4	0	0	Died
*‡41	7.7	M	4/52	3	Rubeola	0	102/58	1-4	2	3	7/52
42	9.3	F	6/55	28	0	0	104/60	2-2	1-3	0	7/56
43	4.4	F	6/53	3	0	+	90/60	4-4	3-5	0	4/56
44	4.6	M	6/54	40	URI	+	86/40	2-4	0	0	8/56
45	3.3	F	3/53	28	0	+	110/70	1-2	0	2-4	4/55
46	7.5	M	10/55	12	URI	+	110/36	3-4	0	0	6/56
‡47	2.3	F	3/52	14	URI	+	92/60	0-4	5-50	2-7	7/52
*48	3.6	M	12/51	5	0	+	80/20	4-4	20-30	3-4	6/54
*49	5.0	M	6/53	104	URI	+	110/80	4-4	0	0	5/56
50	4.5	M	9/55	24	URI	+	110/70	4-4	2-15	1-5	6/56
51	8.6	F	7/55	36	0	0	110/62	1-4	Many	0	4/56
52	1.3	M	11/52	40	0	+	108/56	4-4	0	1-4	5/56
53	12.7	F	8/55	6	0	+	110/78	4-4	10-120	1-5	6/56
54	0.3	M	12/55	1.5	URI	+	130/68	4-4	0	2-6	Died

* In earlier series mechlorethamine hydrochloride, 0.3 or occasionally 0.2 mg. per kilogram, was given at the start of corticotropin administration.[4]

† These patients were given a 6%-20% solution of dextran in water for a total of 100 to 5000 cc. prior to corticotropin therapy.

‡ Identifies patients who received brief courses of corticotropin or cortisone in small dosage at other hospitals.

Of the 72 patients admitted during the initial attack of nephrotic syndrome 60 had dependent edema or anasarca. The incidence was about the same in the exacerbations, 83%, even though the diagnosis was presumably made sooner. The highest blood pressures recorded during the one to two weeks of observation prior to corticotropin therapy are given in Tables 1A and 1B. With the exception of six patients, the highest systolic reading was 110 mm. Hg. In these six the systolic blood pressure was 120, 120, 124, 130, 130, and 130, in Patients 22, 32, 38, and 54 (Table 1A) and 59 and 72 (Table 1B). The diastolic readings were 80 mm. Hg or lower in all but Patient 38 (82 mm.) and Patient 59 (100 mm.), both of whom have already been cited as having high systolic values.

Albuminuria (heat and acetic-acid test) was present of course in all 106 instances of nephrotic syndrome. This ranged up to 4+ during the initial episode in all but six patients and in all but four exacerbations. In slightly more than one-half of the initial attacks microscopic hematuria was found in one or more of the pretreatment urine analyses. This was much less frequent, 18%, in the recurrences. Urinary casts, granular, cellular, or waxy, also occurred more frequently during the initial attacks (Tables 1A and 1B).

In the hospital therapy has consisted of 100 and occasionally 200 mg. of corticotropin * in divided dosage, given daily for four weeks usually without

* Dr. G. Martin and the National Drug Company provided supplies of corticotropin (ACTH).

TABLE 1B.—*Clinical Findings in Eighteen Initial Episodes and Thirty-Four Exacerbations of Nephrotic Syndrome in Eighteen Children*

Patient	Age, Yr.	Sex	Onset Date (Mo./Yr.)	Duration of Symptoms, Wk.	Course	Antecedent Infection	Edema	Blood Pressure at Rx	Albumin (0-4+)	RBC, No./HPF	Casts, No./HPF	Last Seen (Mo./Yr.)
†55	2.9	F	12/54	1.6	1	0	+	90/30	0-4	5-25	1-2	4/56
					2	URI	+		1-1	0	Rare	
†56	1.8	M	8/55	20	1	URI	+	100/58	0-4	0	0	8/56
					2	0	+		4-4	0	0	
57	11.5	M	1/51	8	1	0	+	104/50	4-4	2-100	1-12	
					2	0	+		4-4	1-40	1-6	10/54
†58	3.0	M	6/54	2	1	0	+	92/60	4-4	Rare	Rare	5/56
					2	0	+		4-4	0	2-7	
†59	9.8	F	5/54	84	1	0	+	120/103	0-4	4-15	0	7/56
					2	0	0		4-4	1-2	1-3	
60	1.3	F	10/53	5	1	0	+	96/46	4-4	1-2	1-2	1/55
					2	0	+		Tr.-4	0	Rare	
					3	URI	+		4-4	5-15	1-2	
61	3.2	M	3/55	11	1	URI	+	100/60	4-4	2	0	8/56
					2	0	+		1-4	0	0	
†62	3.5	F	1/55	14	1	URI	+	90/30	0-4	0	Rare	5/56
					2	URI	+		0-4	0	0	
†63	2.7	F	8/53	5	1	URI	+	100/50	3-4	1-7	1-4	4/56
					2	0	+		4-4	2-3	1-3	
					3	URI	+		4-4	0	0	
*†64	1.9	M	12/52	8	1	URI	+	79/49	4-4	0	1	5/56
					2	URI	+		0-4	2	0	
					3	0	+		0-4	0	0	
*65	3.6	M	6/50	52	1	0	+	82/40	0-4	10-100	2	3/56
*					2	0	0		4-4	0	0	
					3	URI	0		0-1	0	Rare	
					4	0	0		1-4	0	0	
					5	0	0		0-4	0	0	
*					6	0	0		1-3	0	2-4	
					7	0	+		4-4	0	0	
66	2.5	M	9/54	7	1	Varicella	+	100/60	3-3	0	0	5/56
					2	URI	+		4-4	0	0	
67	1.8	F	/52	156	1	0	0	92/30	0-4	0	4-5	2/56
					2	0	+		0-4	3-9	0	
					3	URI	+		Tr.-4	0	1-3	
*68	2.4	M	7/52	24	1	URI	+	96/30	0-4	0	2-3	4/56
					2	0	+		0-4	0	Rare	
					3	0	+		0-4	0	0	
*					4	URI	+		Tr.-4	0	0	
					5	URI	+		0-4	0	0	
					6	URI	+		Tr.-4	0	1-2	
*69	1.1	M	6/53	4	1	Pharyn.	+	100/56	0-4	0	1-4	6/56
					2	0	+		4-4	0	0	
					3	0	+		4-4	0	6-12	
70	1.2	F	5/54	1	1	0	+	100/60	4-4	0	0	6/56
					2	0	+		0-4	0	0	
					3	0	+		4-4	0	0	
71	8.4	M	10/55	1.5	1	0	+	100/60	1-3	0	0	1/56
					2	0	+		1-3	0	0	
72	2.0	M	1/54	1.5	1	URI	+	130/68	4-4	0	0	6/56
					2	URI	+		0-4	0	Rare	
					3	Bronch.	+		0-4	0	0	

* In earlier series mechlorethamine hydrochloride, 0.3 or occasionally 0.2 mg. per kilogram, was given at the start of corticotropin administration.[6]

† These patients were given a 6%-20% solution of dextran in water for a total of 100 to 500 cc. prior to corticotropin therapy.

‡ Identifies patients who received brief courses of corticotropin or cortisone in small dosage at other hospitals.

interruption during maintenance on diets containing 2 to 9 mEq. sodium and 150 mEq. potassium and on prophylactic penicillin or other antibiotics, supplementary iron, and vitamins. Patients in the earlier series who received dextran, polyvidone, or mechlorethamine hydrochloride (nitrogen mustard) are identified in Tables 1A and 1B.[6] None of these agents has been used in the last 42 patients in our series. The composition of the diet and the details of the therapeutic regimen have been described in an earlier publication.[6] In accordance with the custom of Lange and others,[9] children who had one or more exacerbations were re-treated and placed on intermittent or continuous prophylactic therapy (100 or more units of corticotropin, up to 400 mg. of cortisone, or up to 30 mg. of prednisone on a variable schedule) as outpatients. In these instances the dietary intake of sodium has not been rigidly restricted.

Results

A. Changes in Proteinuria and Edema

1. Proteinuria: In Figures 1 and 2 the degree of proteinuria during each week (heat and acetic-acid test of daily urine samples with results rated on a scale of zero to 4+, averaged, and expressed as a single mean value) prior to, during, and following corticotropin therapy are presented for the initial attacks and exacerbations, respectively. According to the mean values recorded during the first week following completion of the course, treatment reduced the degree of proteinuria to 1+ or lower in 65% of the initial attacks and in 86%

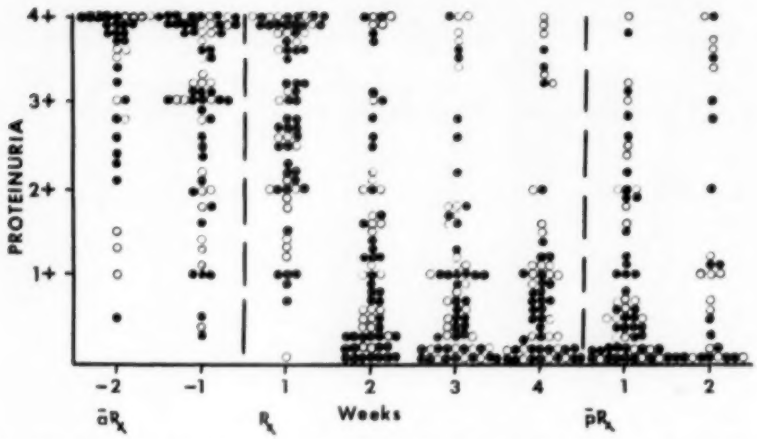

Fig. 1.—Decrease in proteinuria during corticotropin therapy of initial episodes of nephrotic syndrome in children. Solid circles identify boys.

of the exacerbations. The trend to decreased losses of urinary protein was well established by the second week of treatment. At the end of therapy and during the first and second week thereafter a minority of patients still showed proteinuria in excess of 1+. The number with persistent proteinuria was reduced to a minimum of 8 children out of the 72 one to six months thereafter without further therapy.

In the exacerbations (Fig. 2) pretherapy proteinuria declined as promptly, and to a comparable degree, as in the initial episodes shown in Figure 1.

2. Edema: As indicated in Tables 1A and 1B, localized or generalized edema was present on admission in 92 of the 105 cases. In 36 of these 92 the edema decreased or disappeared on a low-sodium diet (Table 2) with or without dextran or polyvidone therapy (Tables 1A and 1B) prior to corticotropin administration. Of the remaining 56 there was no change in 45 and the edema actually increased despite sodium restriction in 5 patients; in the 6 others definitive information on this point was lacking.

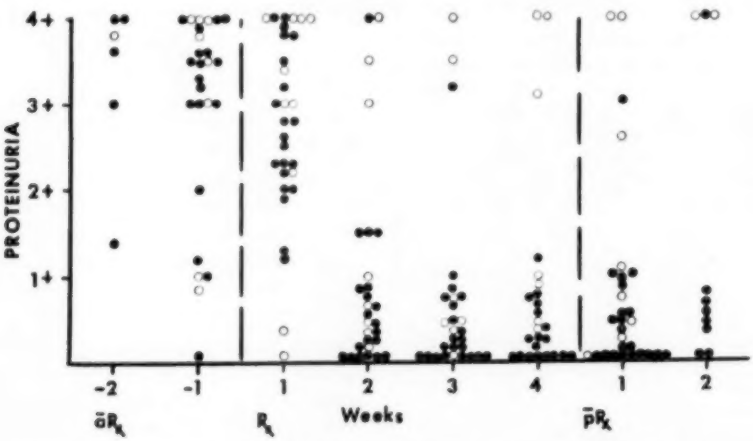

Fig. 2.—Effect of corticotropin on proteinuria in subsequent exacerbations of nephrotic syndrome.

TABLE 2.—*Edema in Nephrotic Syndrome Prior To, During, and Following Corticotropin Therapy*

	Patients, No.	
I. No edema on admission*	14	
II. Edema on admission†	92	
A. Edema decreased before corticotropin	31	
B. Edema completely gone before corticotropin therapy	5	
C. Edema increased before corticotropin	5	
D. Edema unchanged before corticotropin	45	
E. No information	6	
III. At end of corticotropin therapy		
A. Edema all gone	65	
1. Weight decreased		47
2. Weight increased		15
3. Weight unchanged		3
B. Edema improved but not all gone	11	
C. Edema still present and not changed	4	
D. No information	12	

*Also did not develop edema during therapy.
† Nineteen of these patients, all in an earlier series, received dextran as a 6% to 20% solution in water for a total of 100 to 5000 cc. prior to the start of corticotropin therapy. The results have been presented in detail in another publication,[8] and the patients are identified in Tables 1A and 1B.

At the end of corticotropin therapy all evidence of edema had disappeared in 65 of the original 92, was greatly reduced in another 11, and was unchanged in only 4. None of these for whom adequate data were recorded had become worse, though sufficient information is lacking on 12 others. These findings, together with evidence that in a small group of patients, 15 in number, body weight had increased simultaneously with delivery of the edema, are summarized in Table 2. This rise in body weight in all probability resulted from a gain in flesh.

B. Changes in Blood Pressure and Occurrence of Side-Reactions and Complications

The cases have been divided into two groups: those in whom corticotropin therapy was undertaken and concluded without interruption and those in whom treatment was stopped prematurely or discontinued for a few days, for one of a variety of reasons to be discussed later.

1. Blood Pressure: The blood pressure usually increased during corticotropin therapy. In this evaluation we have used the maximal and minimal systolic and diastolic blood pressures obtained at bed rest before breakfast during each day of the two weeks prior to therapy as a base line for comparison with readings recorded daily during the four weeks of corticotropin administration. Changes greater than 10 mm. of mercury were considered significant.

From Table 3 it is evident that corticotropin administration raised the maximal systolic blood pressure in 75.3% and 58.8% of the children in the uninterrupted and interrupted groups, respectively. The average increase during uninterrupted courses was 31 mm. mercury, with a range of +12 to +68. In the remainder the blood pressure did not change more than ± 10 mm.

TABLE 3.—*Maximum and Minimum Systolic and Diastolic Blood Pressure Findings During Corticotropin Therapy*

	Blood Pressure					
	Maximum			Minimum		
	Decr. Below −10 Mm.	−10 to +10 Mm.	Incr. Above +10 Mm.	Decr. Below −10 Mm.	−10 to +10 Mm.	Incr. Above +10 Mm.
Systolic pressure uninterrupted						
No.	3	18	64	0	28	47
Mean	−22		+31.3			+19.9
Range	14–32		12–68			12–72
% of Total	3.5	21.2	75.3	0	44.7	55.3
Interrupted *						
No.	0	7	10	2	11	14
Mean			+24	−14		+19.2
Range			16–30	14–14		12–27
% of Total	0	41.2	58.8	11.8	64.7	23.5
Diastolic pressure uninterrupted						
No.	4	25	56	10	49	26
Mean	−16.5		+26.8	−19.4		+21.7
Range	12–20		12–50	14–34		12–38
% of Total	4.7	29.4	65.9	11.8	57.6	30.6
Interrupted						
No.	1	5	11	2	9	6
Mean	−12		+26.5	−12		+26
Range			12–52	12–14		14–48
% of Total	5.9	29.4	64.7	11.8	52.9	35.3

* Series in which therapy was interrupted for lack of corticotropin supplies or concern about an untoward reaction; only blood pressure readings obtained prior to such interruptions are included in the Table.

TABLE 4A.—*Complete List of Complications and Side-Reactions* Exclusive of Hypertension Occurring During 106 Courses of Corticotropin Therapy*

None	68
Personality change	1
Generalized convulsions	7 in 6
Gastroenteritis	5
Upper respiratory infection	5
Bronchitis	5
Pneumonia and moniliasis	1
Moniliasis oral	1
Stomatitis and parotitis	1
Abscess	1
Peritonitis	1
Septicemia and pneumonia	1
Rubeola	1
Herpes and stomatitis	1
Fever	3
Fever and epistaxis	1
Tachycardia	2
Dyspnea	1
Systolic murmur	1
Steroid diabetes	1

* Forty in thirty-eight patients.

or an actual decrease was recorded. Similar increases were usually recorded, though not as often or as great, in the minimal systolic and the maximal and minimal diastolic pressures. The frequency of these and the other changes and their extent are shown in Table 3. The increases in bood pressure were not per se considered as contraindications to continuation of therapy. The possible relationship of blood pressure changes to the convulsions which appeared in six of the children are discussed in the section which follows.

2. Side-Reactions and Complications: The development of a moon face, buffalo hump, freckling, and acne was recorded in virtually all of the patients. The rounding of the face cannot be assigned solely to corticotropin therapy, because the patients developed voracious appetites and gained flesh on the low-sodium high-potassium diet. In Table 4A the untoward events exclusive of hypertension which occurred in the 106 cases treated with corticotropin are listed. The other 68 courses proved uneventful.

There is no reason to suppose that the gastroenteritis and related symptoms listed in Table 4A can be attributed to corticotropin. Moniliasis, occurring in two patients, may have been related to the penicillin therapy. The other infections, bacterial and viral, do not appear to have been more frequent than one might expect in a similar group of nephrotic children not under corticotropin therapy.

Only the one instance of transient steroid diabetes, the seven generalized convulsions, and the single change in personality may be reasonably considered to have been complications of corticotropin therapy.

The duration of therapy, antecedent and concurrent blood pressure readings, and results of blood and serum analyses in the patients who developed these C. N. S. signs are summarized in Table 4B.

With one exception the convulsions occurred during the fourth week of therapy; in one case the seizure developed on the day following completion of the course. In Patient 40 the second convulsion appeared three days following resumption of therapy after a three-week period without corticotropin. All six patients had distinct systolic or diastolic hypertension, or both, during the week preceding the seizure. None had uremia in the usual clinical sense, though the whole blood NPN was 50 mg/100 cc. in Patient 57. In three of the patients the results of recent blood and serum analyses were within the range usually seen in nephrotic syndrome. Hyponatremia was present in two others, and one patient had hypocalcemia. Other changes as noted in Table 4B included hypochloremic alkalosis in two patients with an associated hypokalemia in one of these. Five of the patients recovered without sequelae from the seizure. The sixth, Patient 7, was in respiratory failure for several minutes and has never regained normal intellectual function, though the nephrotic syndrome has cleared. One patient of this group, Patient 40, subsequently died in far-advanced renal failure.

The one patient, Patient 41, who developed a mild depression had received corticotropin for 21 days. The patient returned to her pretreatment status one week after withdrawal of corticotropin.

C. Clinical Course and Current Status of the Seventy-Two Children with Nephrotic Syndrome

TABLE 4B.—*Blood Pressure and Blood and Serum Solutes in Seven Convulsive Episodes and in One Patient with Personality Change*

Patient	Duration of Corticotropin Rx, Days	Date of Episode	B.P. at Episode*	B.P. Dur. Episode	Date	Blood		Serum									Comment
						Sug. Mg/ 100 Cc.	NPN Mg/ 100 Cc.	HCO_3 mEq/ L.	Cl mEq/ L.	Na mEq/ L.	K mEq/ L.	Ca Mg/ 100 Cc.	Phos. Mg/ 100 Cc.	Alb. Gm/ 100 Cc.	Glob. Gm/ 100 Cc.	Chol. Mg/ 100 Cc.	
19	26	6/2/54	136–94	150/130	6/2/54	129	44	24.7	102.7	142	4.4		5.66			600	
			90–52		6/3/54	74	31	26.2									
18	25	6/21/55	160–122	142/124	6/22/55	61	37	29.2	92.5	142	4.9	10.6	5.66	4.03	2.92	314	Hypochloremic alkalosis
			124–70														
7	28	7/9/52	130–100	155/125	7/ 2/52	106	32	24.8	99.6	143	3.6	9.4		3.38	3.42	338	
			100–50		7/ 3/52									2.76	2.49	333	
57	24	7/31/52	146–100	180/120	7/ 9/52	117	22	31.3	66.1	112	2.3	10.17	2.3	3.08	1.66		
					7/31/52	100	50	29.2	90.0	141.8	2.4	5.5	3.87	2.39	2.42		Early renal failure, hypocalcemia, hypokalemia, alkalosis, hypochloremia
			100–70		7/31/52	164	53	26.8	92.2	141	2.0		2.31				
15	22	7/5/55	184–110	170/140	7/5/55		18	24.3	101.2	147	4.1	9.4	4.45	3.03	3.0	229	
			90–60														
40 (first)	22	1/6/53	162–118	164/122	1/6/53	176	36	17.0	101	113.5	5.9	8.20	5.93	1.09	1.75		Hyponatremia
			110–64														
40 (second)	3	2/1/53	130–124	210/110	2/1/53			7.5	101.8	125	5.2			.76	1.69		Renal failure
			90–68		2/2/53	123	56										
Personality change:			130–110	140/80													
41†	21	6/5/54	90–44		6/5/54	80	45	14.2	98.2					2.54	2.55	259	

* Numerator refers to range of systolic blood pressure during week before episode; denominator refers to range for diastolic pressure.
† Personality change consisting of flattening of affect.

TABLE 5.—*Clinical and Laboratory Data in Four Fatal Cases of Nephrotic Syndrome* *

Patient	Age, Yr.	Sex	Onset (Mo./Yr.)	Corticotropin, Mg. (Date)	Cortisone, Mg. (Date)	Died (Date)	Blood and Sugar Solutes						Autopsy Findings
							Date	NPN, Mg/100 Cc.	CO_2 mEq/L.	Cl, mEq/L.	Na, mEq/L.	K, mEq/L.	
34	0.3	M	12/55	100 q. d. (1/10/56-2/7/56)		3/12/56	3/6/56	37	17.6	111	142	4.0	Subacute glomerulonephritis; acute bronchopneumonia
38	1.5	M	4/54	100 q. d. (2/26/56-2/29/56) 100 q. d. (5/20/54-6/13/54)		6/25/54	6/24/54	29	26.1	87.5	125	4.7	No autopsy; blood culture: Staph aureus; bilateral bronchopneumonia; purpura
21†	0.5	F	10/47	100 q. d. (1/11/51-1/20/51)	300 q. d. (1/11/51-1/20/51)	1/26/51	1/25/51	97	15.4	84			Chronic glomerulonephritis (nephrotic stage); bronchopneumonia; endocardial sclerosis
40†	3.0	M	11/52	100 q. d. (12/15/52-2/1/53)		4/28/54	4/24/54	263	7.5	80	126	6.8	Chronic glomerulonephritis (uremia); uremic pneumonitis; petechiae of midbrain, penis, and GI tract

* Proteinuria not affected by therapy in any of these patients.
† Patient 21 had NPN of 42 on first day of corticotropin therapy; Patient 40 had NPN of 22 and 25 mg/100 cc. prior to and following corticotropin course two years before death.

TABLE 6.—*Summary of Current Status of Seventy-Two Children with Nephrotic Syndrome*

72 Patients

Dead: 4
1. Patient 38
2. Patient 40
3. Patient 54
4. Patient 21

Living: 68

No info. on following for 12 mo. or longer
1. Patient 8*
2. Patient 12*
3. Patient 24*
4. Patient 27*
5. Patient 48*
6. Patient 45*
7. Patient 47*

Persistent albuminuria (1+ to 4+) after 1 or more courses of corticotropin

Without Maint.	With Maint.
1. Pt. 5	1. Pt. 67
2. Pt. 35†	2. Pt. 13
3. Pt. 22	3. Pt. 51
4. Pt. 17‡	4. Pt. 23†
5. Pt. 57†	5. Pt. 59
6. Pt. 41†	

Entirely well after 1 course of corticotropin

Without Maint.		With Maint.	
1. Pt. 2	15. Pt. 36	Corticotropin (100mg. 3×/week)	Cortisone (400mg. 3×/week)
2. Pt. 4	16. Pt. 39	1. Pt. 42	1. Pt. 3
3. Pt. 6	17. Pt. 43	2. Pt. 46	
4. Pt. 9	18. Pt. 44	3. Pt. 1	
5. Pt. 10	19. Pt. 50		
6. Pt. 11	20. Pt. 53		
7. Pt. 15	21. Pt. 71		
8. Pt. 16	22. Pt. 10		
9. Pt. 18	23. Pt. 31		
10. Pt. 25	24. Pt. 29		
11. Pt. 20	25. Pt. 30		
12. Pt. 32	26. Pt. 49		
13. Pt. 26	27. Pt. 52		
14. Pt. 33	28. Pt. 14		

Entirely well after 2 or more courses of corticotropin

Without Maint.
1. Pt. 28
2. Pt. 7
3. Pt. 61

With Maint.

Corticotropin (100mg. 3×/week)	Cortisone (400mg. 3×/week)	Prednisone (30 mg. daily)
1. Pt. 55	1. Pt. 34	1. Pt. 70
2. Pt. 62	2. Pt. 56	
3. Pt. 66	3. Pt. 58	
4. Pt. 68	4. Pt. 37	
5. Pt. 63	5. Pt. 64	
6. Pt. 69	6. Pt. 65	
	7. Pt. 72	
	8. Pt. 60	

* Indicates patients who were entirely well when last seen.
† Identifies patients with NPN of 40 mg/100 cc. or higher. Each of these had known albuminuria for years.
‡ Identifies two patients who responded to initial course with complete remission but not to subsequent re-treatment on maintenance therapy.

Four of the seventy-two patients have died to date: Patient 21 (renal failure, endocardial sclerosis, and bronchopneumonia), Patient 38 (Staphylococcus septicemia), Patient 54 (bronchopneumonia), and Patient 40 (renal failure). Their clinical course and the details of therapy are given in Table 5. None of these died during the period of therapy.

In 28 of the original 72 children a single course of therapy sufficed to bring about a complete remission in the clinical and laboratory manifestations of the nephrotic syndrome which has lasted up to the present (Table 6). Seven other children were free of albuminuria after one course, but there has been no follow-up within the past 6 to 12 months. In an additional 3 children of the original 72 an initial complete remission was followed by an exacerbation which responded to retreatment.

Hence, of the 68 living patients about one-half (31 and possibly 38) have remained well after one or more courses without maintenance therapy. Maintenance dosages of corticotropin, cortisone, or prednisone‡ as shown in Table 6 have been given to 19 of the 68 living children, and all of them are well. It is not certain, of course, that such maintenance therapy was needed in each case. Nonetheless, out of the original total of 72 children a maximum of 57 are apparently well at present. Eleven of the children continue to have albuminuria, including two who had responded completely at one time; three had azotemia before therapy and still have elevated nonprotein-nitrogen levels. Two of the last group have hypertension. The duration of observation in the entire group has been summarized in Table 7.

Comment

Initially corticotropin and cortisone were used only for the production of diuresis, though it was noted that remissions lasting up to several months in length were induced

‡ Organon, Inc., through Dr. K. W. Thompson, provided much of the prednisone used in these studies.

TABLE 7.—*Period of Observation Following the First Course of Corticotropin to the Last Clinic Visit*

Years	Patients, No.	Died
6 to 7	1	
5 to 6	3	
4 to 5	5	
3 to 4	10	
2 to 3	11	
1 to 2	18	Patient 40
Less than 1	24	Patients 21, 54, and 38

in some of the children.[1-7] The dosages of these agents were often small, ranging as low as 20 mg. of corticotropin and 40 mg. of cortisone a day, and the duration of therapy was limited to several days. These schedules arose from a combination of the initially limited supplies of the drugs and inability to control the sodium retention and edema which were provoked by increased therapy. The low-sodium high-potassium regimen both eliminates the latter objections and makes feasible the administration of larger amount for prolonged periods of time. This, in turn, permits an attack upon the underlying disease rather than upon its symptomatology.

The regimen requires adequate supervision and the knowledge and facilities for meeting emergencies such as hyponatremia and water intoxication convulsions and requires an awareness of the risk of hypertension and overwhelming infection.

Our period of observation is as yet too short to be certain that intensive therapy does alter the course of the underlying disease in addition to rendering the patient symptom- and sign-free. The mortality to date, compared with that in control series assembled prior to the availability of corticotropin and adrenocortical steroids (Table 8), suggests that the regimen as a whole probably prolongs life. There are, however, two distinct limitations in the available control data: First, most workers have excluded from their series of lipoid nephrosis those children who had hypertension, microscopic hematuria, or azotemia together with the massive proteinuria or other manifestations of the nephrotic syndrome. These patients who were labelled as nephritic might be expected to show, of course, a decreased survival and increased mortality and if included in the gross category of nephrotics would make the prognosis even more grave. As pointed out earlier, we have not excluded any cases from our group for this or any other reason, but it is possible that the outside physicians may have done so by not referring nephritics or far-advanced renal failures to us. Second, the reported series which cover a decade or longer either antedated the chemotherapeutic-antibiotic era or partially overlapped it. Deaths from infection therefore compromise the ultimate outcome with respect to the renal disease per se. We have summarized some of these reports in Table 8 for comparison with our corticotropin- and antibiotic-treated group.[11-21]

Only adequate follow-up will determine whether the children in our series who have had complete resolution will remain well and will not develop chronic nephritis. One can hope that the experience with acute glomerulonephritis will be repeated, i. e., once a cure has been achieved the patient is not subjected either to recurrences or to chronic nephritis.[22-24]

Summary and Conclusions

Seventy-two children have received 106 courses of corticotropin (ACTH) in treatment of the nephrotic syndrome; these were consecutive admissions, and cases with hypertension, azotemia, and formed elements were not excluded.

Corticotropin, with a low-sodium high-potassium, antibiotic, vitamin, and iron regimen, given for 28 days produced a remission in all but 9 of the 68 children who are still living. The nine who failed to respond at least once included three patients with chronic azotemia.

Two-thirds of the patients have been followed one year or longer, and 30 of these have been followed for two to seven years.

Within this period there have been four deaths, none of which occurred during corticotropin therapy; one patient died with

TABLE 8.—*Outcome of Nephrotic Syndrome in Reported Series*

Author & Ref.	Interval	No. of Pts.	Selection	Over All Mortal.*, %	Deaths Due to Infect., %	Cont'd Renal Dis., %	Full Recov., %	Duration of Follow-Up, Yr.
Tappan [11]	1912–1931	45	Nephr. syndrome in 15.3% of 339 pts. with renal disease; hematuries not excluded	51.1	52.2	31.1	17.7	0.5–10.5
Schwarz, Kohn, & Weiner [12]	1923–1943	40	Nephrosis when "course. . . not. . . glomerulonephritis"	55.0	100	75	25	7–20 in 8 pts.
Heymann & Startzman [13]	1934–1946	34	"not included cases of primary nephritis which led to a secondary nephrotic syndrome"	29.4	100	2.9	66.7	1–17 in 12 pts.
Block, Jackson, Stearns, & Butsch [14]	1933–1948	40	"who eventually showed evidence of chronic nephritis. . . excluded"	35.0	57.1	26.9	47.5	1–16
Briant, Macdonald, & Solow [14]	20 yr.	28	Excluded those with hematuria, azotemia, or hypertension at start	50.0	35.7	35.7	64.3 †	0.5–2.5+
Barness, Moll, & Janeway [15]	1926–1948	107	Limited to pts. without hypertension and azotemic less than 1 mo.	42.1 ‡		29.0	41.1	7.6 (av.)
Kohn & Obrinsky [17]	26 yr. (ending 1952)	57	Probably no selection (see earlier paper, Ref. 11)	63.2	52.8		14.0	4–26 in 21 pts.
Barnett, Lauson, & Forman [18]	1946–1951	35§	With or without hypertension, hematuria, azotemia; normal sp. gr.	20.0			25.7	5
Galan [16]	10 yr. (ending 1949)	84	Nephrotic symptoms in 83%	25.5 before sulfonamide + antibiotics 13.5 after sulfonamide + antibiotics				
Philips, Calvin, & Kagan [21]	1944–1950	29	Unselected	20.7		13.9	65.5	all cases in 1944–1950 series
This series	1951–1956	72	Unselected	5.6	4.2	13.8	80.6	Table 7, this paper

* Stress mortality of 75% in those with more than minimal hematuria.
† Including six patients followed only 0.5–2.5 years.
‡ If "nephritis-nephrotic stage" is included, total number is increased to 136 and mortality is 49.3%.
§ Total series of 50; 35 followed 1946 through 1951.

terminal uremia, in two others bronchopneumonia was present at death together with moderate azotemia and endocardial sclerosis in one; a fatal Staphylococcus aureus septicemia with purpura developed in the fourth.

Twenty patients have had one or more recurrences after an initial satisfactory response, and eighteen are again well after re-treatement.

Of the 68 living children 50 are known to be entirely well after one or more courses of treatment, and 7 others were entirely well when last seen, but follow-up within the past six months to one year was not possible.

Serious risks during the 28-day course of corticotropin therapy include infections, personality change, and transient steroid diabetes. Systolic and diastolic hypertension usually appears during treatment and may well be a decisive factor in the occurrence of convulsions. Intermittent maintenance therapy has been uneventful.

The mortality figures to date suggest that there is modification of the underlying course of the disease in addition to control of the symptoms and signs, provided one keeps in mind the custom in many published series of excluding "nephritic" patients. Only adequate follow-up will determine, however, whether patients whose nephrotic syndrome resolves may still develop chronic nephritis.

3630 Terrace St. (13) (Dr. Danowski).

REFERENCES

1. Luetscher, J. A., Jr.; Deming, Q. B., and Johnson, B. B.: Treatment of Nephrosis with Pituitary Adrenocorticotrophin, J. Clin. Invest. 30:1530, 1951.

2. Rapoport, M.; McCrory, W. W.; Barbero, G.; Barnett, H. L.; Forman, C. W., and McNamara, H.: Effect of Corticotropin (ACTH) on Children with Nephrotic Syndrome, J. A. M. A. 147:1101, 1951.

3. Farnsworth, E. B., and Dupee, C. F.: Further Studies on the Effects of ACTH in the Nephrotic Syndrome, in Proceedings of the Second Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1951, Vol. 2, p. 149.

4. Kramer, B.; Goldman, H., and Cason, L.: The Treatment of the Nonedematous Nephrotic Child with ACTH, J. Pediat. 41:792, 1952.

5. Riley, C. M.: Corticotropin and Cortisone in Management of the Nephrotic Syndrome in Children, J. A. M. A. 150:1288, 1952.

6. Metcoff, J.; Rance, C. P.; Kelsey, W. M.; Nakasone, N., and Janeway, C. A.: Adrenocorticotrophic Hormone (ACTH) Therapy of the Nephrotic Syndrome in Children, Pediatrics 10: 543, 1952.

7. Barnett, H. L.: Effect of ACTH in Children with the Nephrotic Syndrome, Pediatrics 9:341, 1952.

8. Greenman, L.; Weigand, F. A., and Danowski, T. S.: Therapy of the Nephrotic Syndrome: Sodium Restriction, Dextran, and Corticotropin (ACTH) Alone or Combined with Nitrogen Mustard, A. M. A. Am. J. Dis. Child. 89:169, 1955.

9. Lange, K.; Slobody, L., and Strang, R.: Treatment of Nephrotic Syndrome with Interrupted ACTH or Oral Cortisone Therapy, Proc. Soc. Exper. Biol. & Med. 82:315, 1953.

10. Merrill, A. J.; Wilson, J., and Timberlake, L. F.: Continuous Therapy of Nephrotic Syndrome in Children with Corticotropin Gel, A. M. A. Arch. Int. Med. 94:925, 1954.

11. Tappan, V.: Prognosis of the Nephrotic Syndrome in Children: A Clinical Study, Am. J. Dis. Child. 49:1487, 1935.

12. Schwarz, H.; Kohn, J. L., and Weiner, S. B.: Lipoid Nephrosis: Observations over a Period of 20 Years, Am. J. Dis. Child. 65:355, 1943.

13. Heymann, W., and Startzman, V.: Lipemic Nephrosis, J. Pediat. 28:117, 1946.

14. Block, W. M.; Jackson, R. L.; Stearns, G., and Butsch, M. P.: Lipoid Nephrosis: Clinical and Biochemical Studies of 40 Children, with 10 Necropsies, Pediatrics 1:733, 1948.

15. Briant, W. W., Jr.; Macdonald, R. R., and Solow, I. A.: Nephrosis: A Survey, Pennsylvania M. J. 51:649, 1948.

16. Barness, L. A.; Moll, G. H., and Janeway, C. A.: Nephrotic Syndrome: I. Natural History of the Disease, Pediatrics 5:486, 1950.

17. Kohn, J. L., and Obrinsky, W.: Lipid Nephrosis in Children: Observations over a Period of 26 Years, A. M. A. Am. J. Dis. Child. 84:587, 1952.

18. Barnett, H. L.; Forman, C. W., and Lauson, H. D.: The Nephrotic Syndrome in Children, in Advances in Pediatrics, Vol. 5, Edited by S. Z. Levine and Others, Chicago, Year Book Publishers, Inc., 1952, p. 53.

19. Friderich, J.; Prader, A., and Fanconi, G.: Incidence, Prognosis, and Treatment of Nephrotic Syndrome, Helvet. paediat. acta 9:109, 1954.

20. Galan, E.: Nephrosis in Children: I. Observations on 84 Patients; II. Clearance and Saturation Tests, Am. J. Dis. Child. 77:328, 1949.

21. Philips, I.; Calvin, J. K., and Kagan, B. M.: Nephrotic Syndrome in Children: Observations on the Clinical Course and the Influence of Sulfonamide and Antibiotic Therapy, A. M. A. Am. J. Dis. Child. 85:451, 1953.

22. Loeb, E. N.; Lyttle, J. D.; Seegal, D., and Jost, E. L.: On the Permanence of Recovery in Acute Glomerulonephritis, J. Clin. Invest. 17:623, 1938.

23. Herbert, H. J.: Acute Glomerulonephritis in Childhood: A Study of the Late Prognosis of 27 Cases, J. Pediat. 40:549, 1952.

24. Seegal, D., and Earle, D. P., Jr.: A Consideration of Certain Biological Differences Between Glomerulonephritis and Rheumatic Fever, Am. J. M. Sc. 201:528, 1941.

Corticotropin (ACTH) Therapy of Nephrotic Syndrome in Children

II. Laboratory Findings in One Hundred Six Instances

T. S. DANOWSKI, M.D.; F. A. WEIGAND, M.D.; LAWRENCE GREENMAN, M.D.†; S. GAILANI, M.D.; W. V. GREENBERG, M.D., and F. M. MATEER, M.D., Pittsburgh

In a previous report we have described the clinical results and the changes in proteinuria in a total of 106 instances of nephrotic syndrome in children treated, usually for 28 days, with corticotropin (ACTH),* 100 to 200 units per day, a very low-sodium high-potassium diet, and penicillin.[1] The alterations in the formed elements of the blood, in serum and blood solutes, and in urinary reducing substances and 17-ketosteroids prior to, during, and following therapy are herein presented.

Materials and Methods

Erythrocyte, leukocyte, and differential blood cell counts; the hemoglobin content; the levels of whole-blood nonprotein nitrogen and sugar; the presence of reducing substances in the urine (Benedict's test); the concentrations of carbon dioxide, chloride, sodium, potassium, total protein, albumin, globulin, calcium, inorganic phosphorus, and cholesterol in serum, and the 24-hour excretion rates of urinary 17-ketosteroids were measured at approximately weekly intervals before, during, and after therapy by methods in regular use in this and other laboratories.[2,3]

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From the University of Pittsburgh School of Medicine and the Children's Hospital of Pittsburgh. Established Investigator of the American Heart Association (Dr. Mateer).

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† Dr. Greenman died June 20, 1956.

* Dr. Gustav Martin and the National Drug Company provided the supplies of corticotropin.

Results and Comment

I. Changes in the Formed Elements of the Blood

In Table 1 the mean erythrocyte, hemoglobin, total leukocyte, polymorphonuclear, and lymphocyte counts; the ranges of these values, and the number of observations prior to, during, and following corticotropin therapy have been recorded. Positive findings were limited to a leukocytosis characterized by an increase in polymorphonuclear cells and metamyelocytes and a decrease in lymphocytes.[4,5] This began during the first week and became maximal during the second, third, and fourth weeks of therapy. The highest leukocyte count observed was 28,000, and the polymorphonuclears rose as high as 96% in patients without infection or any side-reaction or complication while on corticotropin. Though not included in the Table, the same trend and the same magnitude of change were noted in the patients in whom interruption of corticotropin was necessary or deemed advisable for one reason or another.[1] These changes disappeared during the first or the second week following withdrawal of the hormone in both the uninterrupted and interrupted groups.

Comment. Only occasional patients were admitted with elevations in the polymorphonuclear leukocyte count. The trend noted during treatment is in keeping with the well-recognized leukocytosis and lymphopenia evoked by corticotropin alone. Though these changes would be expected in certain infections and probably did occur,

TABLE 1.—*Peripheral Blood Cell and Hemoglobin Changes in Children with Nephrotic Syndrome Prior to, During, and After Twenty-Eight Days of Uninterrupted Corticotropin Therapy*

Week	−2	−1	1	2	3	4	1	2
	Before Rx		During Rx				After Rx	
	Mean (Range) No.	Mean (Range) No.	Mean (Range) No.	Mean (Range) No.	Mean (Range) No.	Mean (Range) No.	Mean (Range) No.	Mean (Range) No.
RBC, million/mm.³	4.05 (3.43–4.52) 26	4.15 (2.18–5.20) 77	4.16 (2.45–14.5) 69	4.19 (2.45–13.5) 70	3.90 (2.72–4.71) 70	4.07 (3.20–12.5) 77	4.20 (2.20–4.82) 67	3.71 (3.10–4.40) 22
Hb, gm./100 cc.	12.1 (8.3–15.0) 24	12.2 (6.3–16.0) 79	11.7 (6.4–15.0) 69	11.4 (6.1–14.7) 67	11.3 (9.0–14.0) 70	11.4 (7.0–14.4) 77	11.4 (8.0–14.7) 70	10.8 (8.7–14.5) 20
WBC/mm.³	8,746 (4,000–16,000) 26	8,248 (3,600–22,950) 77	9,365 (4,000–23,975) 70	12,402 (6,000–24,800) 65	13,272 (6,000–28,000) 73	11,948 (4,050–21,200) 76	8,726 (4,000–25,000) 66	6,887 (3,000–11,550) 19
PMN/mm.³	56.6 (23–92) 19	55.8 (24–95) 81	65.6 (33–91) 69	70.0 (27–94) 63	70.1 (18–89) 71	71.6 (43–96) 71	52.2 (27–94) 62	49.5 (18–81) 23
Metamyelocytes/mm.³	3.2 (2–7) 13	3.6 (1–12) 46	3.6 (1–10) 46	5.2 (1–26) 46	3.8 (1–12) 46	4.3 (1–13) 50	4.3 (1–17) 41	3.3 (1–7) 20
Lymphocytes/mm.³	38.6 (4–65) 19	40.2 (4–70) 80	29.9 (6–67) 67	26.2 (6–44) 63	26.0 (5–66) 71	26.5 (8–66) 73	44.4 (4–68) 61	49.0 (13–76) 21

it is evident that in individual patients the occurrence of polymorphonuclear leukocytosis and lymphopenia cannot be used as indicators of such a complication.

II. Biochemical Changes Prior to, During, and Following Corticotropin

A. The Whole Blood Nonprotein Nitrogen: In measurements obtained one or two weeks before therapy there were 25 elevations of the whole blood nonprotein nitrogen to values above 40 mg/100 cc. (Fig. 1). Though the nonprotein nitrogen rose during the first week of treatment in some of the patients, it fell in an even larger number so that during the second week of corticotropin therapy values of 40 mg/100 cc. or higher were present in only 11. As therapy continued the height of these increases diminished, and during the fourth week only slight increases were present in nine patients. Values in all but two of these dropped below 40 mg/100 cc. following completion of corticotropin administration.

Comment. The precorticotropin azotemia can be presumed to have resulted from a decreased glomerular filtration rate.[6-8] The rises in N. P. N. with institution of therapy are attributable to the antianabolic effects of the steroids.[9-11] The latter were of transient duration because the effect did not continue[12] and/or the renal function improved to a greater degree.

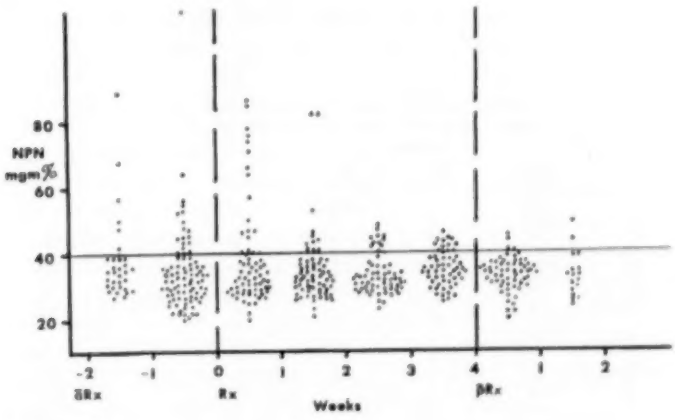

Fig. 1.—Whole blood N. P. N. values before, during, and after corticotropin therapy. The clearance of nonprotein nitrogen improved sufficiently during corticotropin administration to return most values to the normal range despite the increased nitrogen load stemming from greater food intake and the antianabolic effect of 11-oxysteroids.

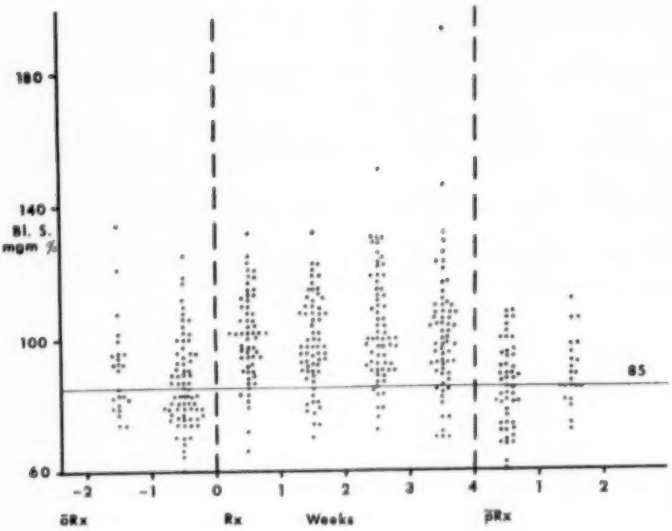

Fig. 2.—Blood sugar levels and corticotropin therapy. The rise in fasting concentrations of glucose in venous blood during therapy produced values above 134 mg/100 cc. on three occasions in two patients (151, 194, and 370 mg/100 cc; the last of these points has not been plotted). The patient with the two higher values developed transient steroid diabetes.

B. Fasting Levels of Sugar in Venous Blood: The fasting blood sugar values increased during therapy (Fig. 2). However, all but three of the higher values were 134 mg/100 cc. or less and therefore within the range recorded in these children as a group prior to corticotropin administration. These three exceptions occurred in two patients, Patient 1 (151 mg/100 cc.) and Patient 2 (194 and 370 mg/100 cc.). In Patient 2 persistent glycosuria was present without ketonuria during the fourth week of treatment. The glycosuria and hyperglycemia both cleared after completion of the course of corticotropin.

Comment. The rise in blood sugar during therapy can be attributed to increased gluconeogenesis [13,14] and an anti-insulin effect,[15] two concomitants of increased adrenocortical activity.

C. Urine Reducing Substances Prior to, During, and Following Corticotropin Therapy: The administration of corticotropin was accompanied by a distinct rise in the incidence of urines sporadically positive for reducing substances (Benedict's test) in both the uninterrupted and interrupted groups. The frequency of this finding and its degree are shown in Table 2. Most of the positive tests were 1+, though occasional 2+, 3+, and 4+ results were recorded. Sufficient data are available on the uninterrupted group to indicate that the increase in reducing substances rapidly dis-

TABLE 2.—*Results of Benedict's Test in Children with Nephrotic Syndrome Prior to, During, and After Uninterrupted and Interrupted Corticotropin Therapy*

		Total No.	Number Neg.	1+ (No.)	2+ (No.)	3+ (No.)	4+ (No.)	1+ or Greater (%)
Uninterrupted								
Before therapy	2d wk.	105	103	1	1	0	0	1.9
	1st wk.	285	279	4	1	1	0	2.1
During therapy	1st wk.	382	365	12	4	0	1	4.4
	2d wk.	400	355	32	8	3	2	11.2
	3rd wk.	386	340	32	8	3	3	11.9
	4th wk.	387	331	36	7	6	7	14.5
After therapy	1st wk.	224	310	8	3	1	2	4.3
	2d wk.	102	94	7	0	1	0	7.8
Interrupted								
Before therapy	2d wk.	19	19	0				0
	1st wk.	43	40	3	0			7.0
During therapy	1st wk.	83	74	5	3	1		10.8
	2d wk.	69	57	8	4	0		17.4
	3rd wk.	52	45	4	0	3		13.5
	4th wk.	23	16	7	0	0		30.4

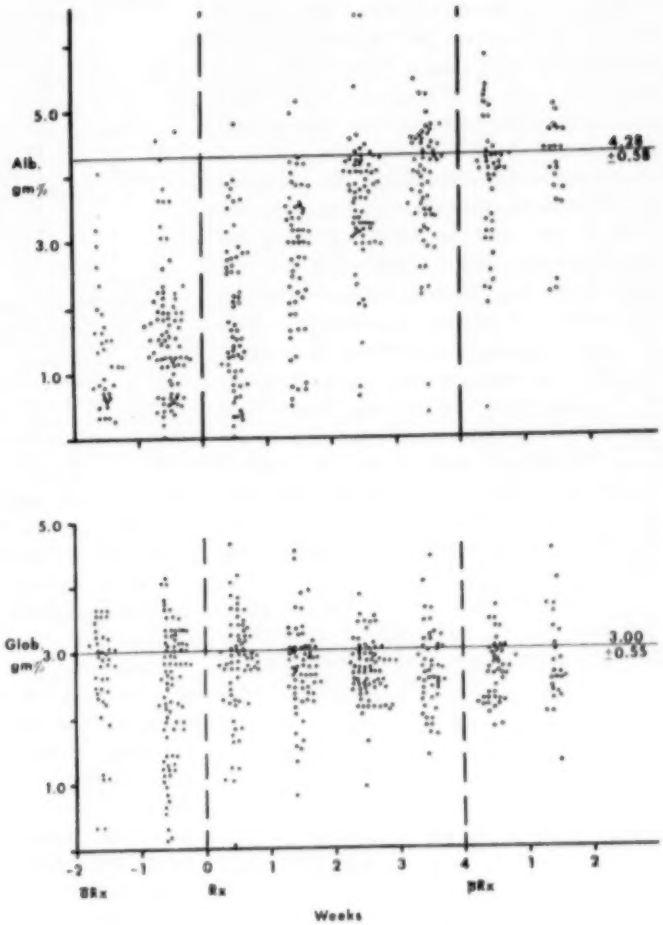

Fig. 3.—Serum albumin and globulin levels in children with nephrotic syndrome. Therapy resulted in a rise in the initially low albumin and globulin concentrations.

appeared in the immediate post-therapy period. These reducing substances were not identified.

Comment. The initial reaction is to ascribe the increased incidence of positive Benedict's tests to a lowering of the $Tm_{Glucose}$ during corticotropin therapy. Such an effect has been reported.[16] However, assuming that the reducing substance was glucose, the available information does not permit differentiation between glucosuria due to decreased tubular reabsorption and that due to postprandial or other hyperglycemia.

D. Serum Albumin and Globulin: The levels of serum albumin prior to treatment ranged from 0.2 to 4.7 gm/100 cc., with most of them considerably below the mean value for healthy children in this age group (Fig. 3). The higher concentrations were present in patients in the earlier phases of the disease or in those in whom a relapse, evident from the reappearance of abnormal urinary findings, had occurred. During the first week of treatment the range of these levels was essentially unaltered, but it rose steadily thereafter in all but a few of the children. At the completion of therapy or one to two weeks thereafter the bulk of the patients fell within the range of normal values.

Though the globulins were not greatly changed in most of the patients prior to therapy, very low values, 1.0 gm/100 cc. or less, were seen in 10 instances. These disappeared during corticotropin administration.

Comment. Children with the nephrotic syndrome ultimately develop hypoalbuminemia if the massive proteinuria persists long enough. Three factors are possibly operative in this: urinary losses of albumin, inadequate net production of this protein fraction even though synthesis is actually increased in most patients,[17] and expansion of the interstitial fluid and the plasma volume.[5,18] The lowering of globulin values is attributable in part to the decrease in complement which is present in this fraction of protein and is known to be lowered regularly in the initial phase and in the exacerbations of nephrosis.[19-21]

E. Serum Cholesterol: The highest value, 1600 mg/100 cc., was found prior to therapy in Patient 3, who had a serum-albumin level of 0.61 gm/100 cc. (Fig. 4). However, this inverse relationship, though common, was not always present (Fig. 5).

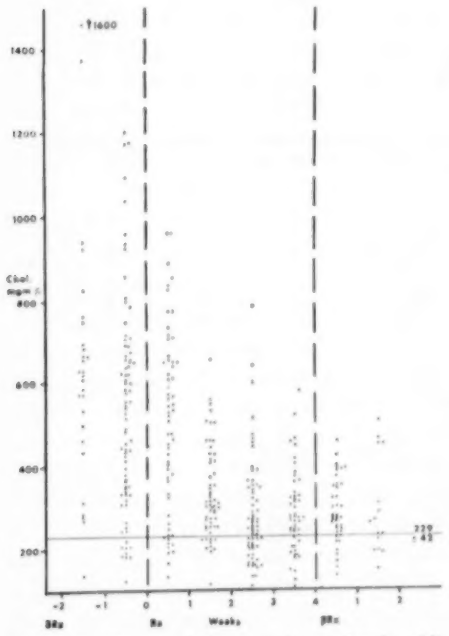

Fig. 4.—Serum cholesterol in nephrotic children. Therapy with corticotropin produced a progressive decrease toward or to the normal range.

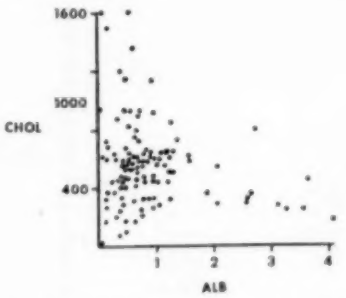

Fig. 5.—Correlation between serum cholesterol and albumin concentrations. Though the greatest increases in cholesterol were obtained in children with the lowest albumin values, moderate hypercholesterolemia was encountered without hypoalbuminemia and marked lowering of serum albumin was unassociated with rises in cholesterol.

During therapy a progressive decline of serum cholesterol toward control values occurred.

Comment. The experimental evidence on the lipid effects of corticotropin and adrenocortical steroids in control subjects is controversial: Decreases[23] as well as increases[24] have been reported after acute therapy; prolonged treatment generally lowers the serum lipids.[25] In our patients it would appear that, in the main, decreases in hypercholesterolemia were related chronologically and perhaps causally to the rise in serum albumin. Though the mechanism of hyperlipemia in nephrosis is not entirely defined, it is probably not related to enhanced absorption of fat or to exogenous fat administration. Increased mobilization or transport of fat is the most likely mechanism, though accelerated synthesis may play a role.[22]

F. Potassium, Bicarbonate, and Chloride: Prior to corticotropin there was a tendency to hyperpotassemia and lowered serum total CO_2 content which persisted during the early weeks of therapy (Fig. 6). Serum bicarbonate rose and chloride fell during treatment, with a return to a more normal distribution after withdrawal of the hor-

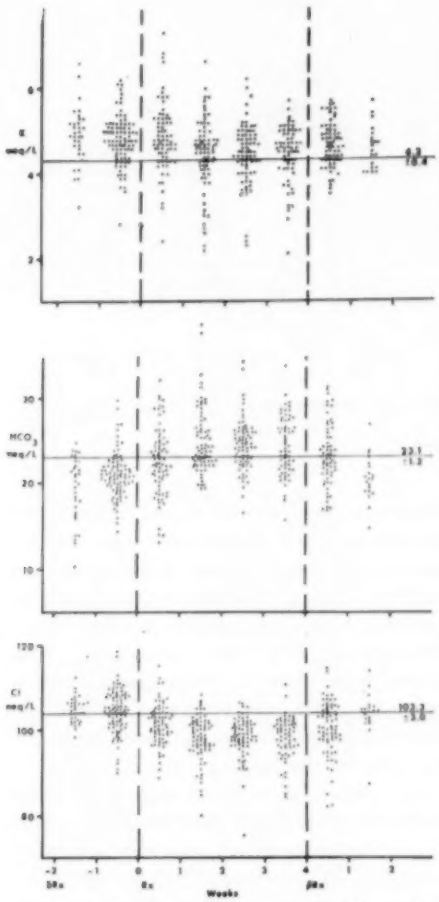

Fig. 6.—Serum potassium, total CO_2 content (HCO_3), and chloride changes. A trend toward hypokalemia and hypochloremic metabolic alkalosis is evident. See text for further comment.

mone. In a small number of patients hypokalemia appeared.

Comment. The initial trend to hyperpotassemia and to lowering of the serum total CO_2 content can be taken to reflect renal failure in some but not all of the patients (Fig. 7). Hypochloremic alkalosis during therapy is usually attributed to depletion of cell potassium,[26] but older as well as more recent studies indicate that cell depletion of this electrolyte can and does occur without hypochloremic alkalosis.[27-29]

G. Sodium: In the untreated state a minority of the patients had hyponatremia, i. e., values below 135 mEq. per liter. These tended to disappear despite the severe sodium restriction of the therapeutic regimen (Fig. 8).

Comment. Decreased concentrations of serum sodium may be present with decreased, intact, or increased extracellular sodium stores.[30] The first of these represents sodium depletion or chronic hypoosmolarity; the second is encountered in water intoxication and in massive hyperlipemia, and the third has been categorized a "new steady state." Hyponatremia occurring in the nephrotic syndrome probably falls into the last of these groups, with hyperaldosteronism playing a role.[31] However, plotting the initial sodium level versus the cholesterol concentrations (Fig. 9) suggests that some or a part of the low-sodium syndromes were attributable to the large

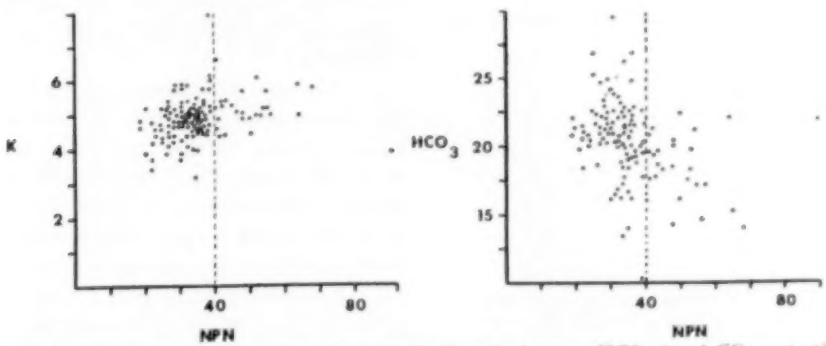

Fig. 7.—Relation of serum K to blood N. P. N. and of serum HCO_3 (total CO_2 content) to blood N. P. N. prior to therapy. Hyperkalemia or lowered serum total CO_2 content were not always correlated with azotemia.

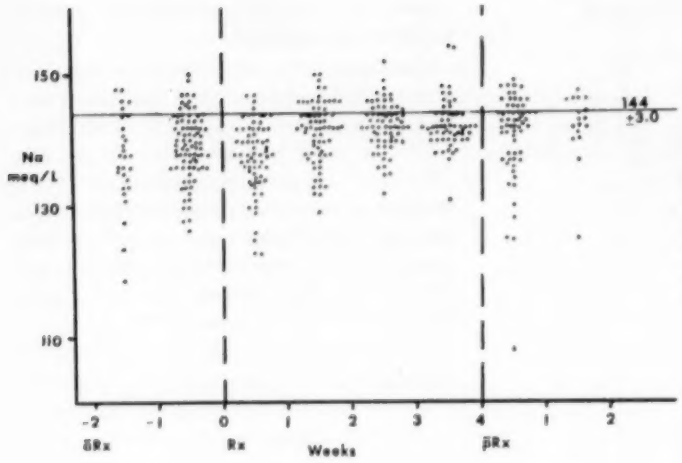

Fig. 8.—Serum sodium levels. Abnormally low sodium concentrations decreased during therapy but did not disappear entirely. See text for etiology of hyponatremia.

proportion of lipid in the aliquot taken for analysis.[32] Finally, chronic malnutrition with resultant cellular hypo-osmolarity may have played a role.[33]

Serum sodium levels were reduced in only two of the six patients who convulsed. These may have been instances of water intoxication, sodium depletion, or both.[30]

H. Calcium and Phosphorus: As therapy progressed the serum calcium values rose steadily from pretherapy hypocalcemic levels. There was very little change following withdrawal of the corticotropin. On the other hand, the serum inorganic phosphorus appeared to have gone through a pendulum-like swing, i. e., high, low, and high (Fig. 10).

Comment. The initially low and subsequently higher calcium values usually correlate with the levels of serum albumin and together with the absence of tetany indicate that the deficit was largely in the un-ionized fraction (Fig. 11). However, it should be noted that in some patients marked hypoalbuminemia was not associated with marked hypocalcemia, suggesting that binding to globulins was occurring or that abnormal albumins were separated with the globulins in the analytic procedure.

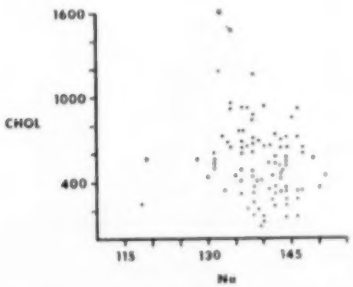

Fig. 9.—Hypercholesterolemia as an infrequent cause of hyponatremia.

In view of the limited degree of renal failure it is unlikely that the high phosphorus values before corticotropin can be attributed to this cause. Some of these probably reflect a reciprocal relationship with the hypocalcemia. The return to high values after therapy suggests that the hormone may have increased the extrarenal segregation or the renal output of this constituent.

I. Urinary 17-Ketosteroid Excretion: The values prior to therapy fell within the limits recorded in this and other laboratories for healthy children.[34] With corticotropin administration a progressive rise in 17-ketosteroid output occurred, reaching levels as high as 116 mg. in 24 hours (Fig. 12). However, patients who did not show a marked increase in 17-ketosteroids still went into clinical remission. This contrasts of course with the correlation of refractori-

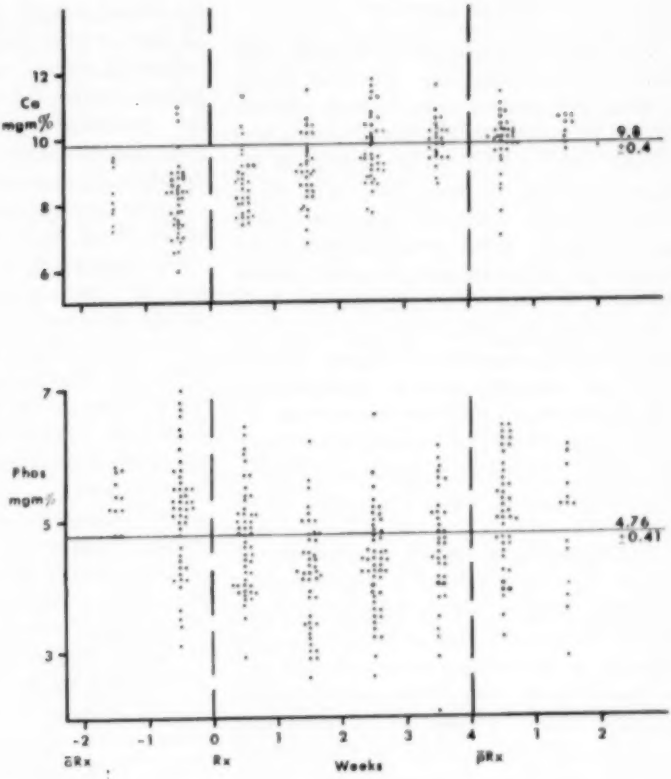

Fig. 10.—Rise in calcium and transient decrease in serum inorganic phosphorus during therapy.

ness to therapy and low compound-F output reported by Farnsworth.[35]

Comment. The urinary 17-ketosteroids are of course only an indirect measure of adrenocortical activity and then predominantly of the androgenic-type steroids. It is possible that the low-sodium high-potassium regimen increases the effectiveness of the corticotropin in discharging the adrenal cortex as a whole, increasing the 11-oxysteroids as well. Animal experiments show that such alterations in the load of these electrolytes augment the size and the function of the adrenal cortices.[36-38]

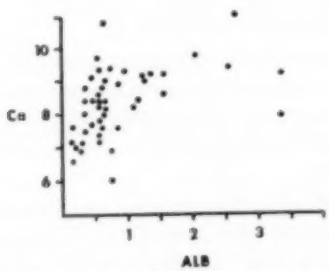

Fig. 11.—Hypoalbuminemia as a cause of hypocalcemia prior to corticotropin administration.

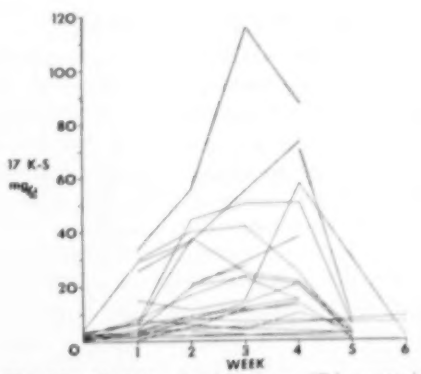

Fig. 12.—Variable rise in urinary 17-ketosteroid excretion during corticotropin treatment.

General Comment

For ease in presentation pertinent comments have already been appended in describing the changes in the formed elements of the blood and in the blood, serum, and certain urine solutes in this group of patients. Survey of these data as a whole permits certain additional statements of a general nature. Thus, since the proteinuria in this group of children was of variable duration, it is not surprising that the laboratory findings of the fully developed nephrotic syndrome were not always present. This was especially true of course in the patients in whom an exacerbation was detected in the course of frequent clinic visits. In these children hypercholesterolemia, hypoalbuminemia, and edema were often lacking.

Furthermore, it should be noted that though trends are evident certain interrelationships between serum solutes need not always be present. Hypoalbuminemia, for example, is not always accompanied by elevations of serum cholesterol; massive hyperlipemia may not produce a detectable lowering of serum-sodium levels; not all patients with hypoalbuminemia have hypocalcemia, etc. These deviations from the expected relationships merely point up the fact that other unidentified variables are operative, altering the synthesis, transport, and degradation of cholesterol and modifying sodium and calcium homeostasis, etc.

Summary and Conclusions

In general, therapy with corticotropin (ACTH) produced certain changes in the absolute and relative numbers of peripheral blood cells, in the solutes of blood and serum, in the output of reducing substances in urine, and in the 24-hour excretion of urinary 17-ketosteroids.

The leukocyte count in peripheral blood rose to an average of 12,000 to 13,000 cubic millimeters during the second, third, and fourth weeks of therapy, reaching values as high as 28,000 without evident infection; during this same period the average percentage of polymorphonuclear cells increased to 72 from a pretreatment range of 56, with individual values as high as 96%; the metamyelocytes increased in number while the lymphocytes fell. Pretherapy values were attained within one week of the termination of corticotropin administration.

About one-quarter of the pretreatment whole blood N. P. N. concentrations were above 40 mg/100 cc., pointing to the presence of a moderate degree of renal failure. By the third week of therapy all values had decreased to less than 50 mg/100 cc. despite the increased nitrogen load which accompanies corticotropin administration. Following completion of the course only scattered slight elevations of the N. P. N. were recorded.

The fasting blood sugar levels increased during therapy and decreased to the pre-corticotropin values at the completion of the course. Concentrations above 134 mg/100 cc. were recorded in only two patients. In one of these the blood sugar of 370 mg/100 cc. and the presence of persistent glucosuria without ketonuria pointed to the presence of steroid diabetes during the fourth week, which disappeared upon completion of the course of corticotropin.

The excretion of unidentified reducing substances in urine increased during therapy.

Hypoalbuminemia present in varying degree in most but not all of the patients was gradually replaced by normal serum albumin values beginning during the second week of treatment; occasional patients also showed marked lowering of the serum globulin values, which disappeared during corticotropin administration.

Hypercholesterolemia was present in most patients; though the elevations of cholesterol concentrations were almost always associated with hypoalbuminemia, the reverse was not true.

Pretherapy decreases in serum total CO_2 content and rises in serum potassium could not always be related to renal failure as reflected by azotemia; during corticotropin

treatment the serum potassium and chloride levels fell while the serum total CO_2 content rose. This pattern of hypokalemia-hypochloremia-alkalosis occurred despite marked restriction of sodium intake.

The tendency to pretherapy hyponatremia was not always associated with hypercholesterolemia, pointing to the existence of hypoosmolarity, undue water retention, or a new steady state as the probable etiology.

Though precorticotropin hypocalcemia disappeared during treatment as the serum albumin rose, the serum calcium levels were not always low in patients with hypoalbuminemia. This suggests binding by globulins or alteration in the physical properties of albumin resulting in their precipitation as globulins. Corticotropin produced a lowering of serum inorganic phosphorus levels which disappeared at completion of therapy.

Though the excretion of urinary 17-ketosteroids usually rose, equally good clinical responses to corticotropin were observed in patients who did not show this change.

3630 Terrace St. (13).

REFERENCES

1. Mateer, F. M.; Weigand, F. A.; Greenman, L.; Weber, C. J., Jr.; Kunkel, G. A., and Danowski, T. S.: Corticotropin (ACTH) Therapy of Nephrotic Syndrome in Children: I. Clinical Results and Effects on Proteinuria in 106 Instances, A. M. A. J. Dis. Child. this issue, p. 591.

2. Danowski, T. S.; Greenman, L.; Mateer, F. M.; Parsons, W. B.; Weigand, F. A.; Mermelstein, H., and Peters, J. H.: Carboxylic Cation Exchange Resin Effects in Dogs, J. Clin. Invest. 30:984, 1951.

3. Holtorff, A. F., and Koch, F. C.: The Colorimetric Estimation of 17-Ketosteroids and Their Application to Urine Extracts, J. Biol. Chem. 135: 377, 1940.

4. Hills, A. G.; Forsham, P. H., and Finch, C. A.: Changes in Circulating Leukocytes Induced by the Administration of Pituitary Adrenocorticotrophic Hormone (ACTH) in Man, Blood 3:755, 1948.

5. Dougherty, T. F., and White, A.: Influence of Hormones on Lymphoid Tissue Structure and Function: Role of Pituitary Adrenotrophic Hormone in Regulation of Lymphocytes and Other Cellular Elements of Blood, Endocrinology 35:1, 1944.

6. Emerson, K. J., and Dole, V. P.: Diodrast and Inulin Clearances in Nephrotic Children with Supernormal Urea Clearances, J. Clin. Invest. 22:447, 1943.

7. Metcoff, J.; Kelsey, W. M., and Janeway, C. A.: The Nephrotic Syndrome in Children: An Interpretation of Its Clinical, Biochemical, and Renal Hemodynamic Features as Variations of a Single Type of Nephron Disease, J. Clin. Invest. 30:471, 1951.

8. Barnett, H. L.; Forman, C. W.; McNamara, H.; McCrory, W. W.; Rapoport, M.; Michie, A. J., and Barbero, G.: The Effect of Adrenocorticotrophic Hormone on Children with the Nephrotic Syndrome: II. Physiologic Observations on Discrete Kidney Functions and Plasma Volume, J. Clin. Invest. 30:227, 1951.

9. Parson, W.; Crispell, K. R., and Ebbert, A., Jr.: Abnormalities in N^{15} Excretion Rates After Ingestion of Tagged Glycine in Cushing's Syndrome and Following ACTH Administration, J. Clin. Invest. 31:548, 1952.

10. Clark, I.: The Effect of Cortisone upon Protein Synthesis, J. Biol. Chem. 200:69, 1953.

11. Albanese, A. A.; Higgons, R. A.; Arnold, W. H., and Hays, D. R.: Effect on ACTH, Cortisone and Salicylates on Protein Synthesis in Man, Fed. Proc. 13:173, 1954.

12. Pearson, O. H., and Eliel, L. P.: Experimental Studies with ACTH and Cortisone in Patients with Neoplastic Disease, Recent Prog. Hormone Res. 6:373, 1951.

13. Long, C. N. H.: The Endocrine Control of the Blood Sugar (Banting Lecture), Diabetes 1:3, 1952.

14. Hausberger, F. X., and Hausberger, B. C.: Over-All Glucose Utilization in Steroid Diabetic Guinea Pigs, Am. J. Physiol. 183:302, 1955.

15. Stadie, W. C.; Haugaard, N., and Marsh, J. B.: The Effect of Growth Hormone and Cortisone on the Action of Bound Insulin, J. Biol. Chem. 198:785, 1952.

16. Reckendorf, H. K.; McGavack, T. H., and Bolukoglu, M. A.: Alterations in Renal Threshold for Sugar by Oral Administration of Cortisone Acetate, Proc. Soc. Exper. Biol. & Med. 90:75, 1955.

17. Kelley, V. C.; Ziegler, M. R.; Doeden, D., and McQuarrie, I.: Labeled Methionine as an Indicator of Protein Formation in Children with Lipoid Nephrosis, Proc. Soc. Exper. Biol. & Med. 75:153, 1950.

18. Chaptal, J.; Jean, R.; Campo, C., and Dossa, D.: The Biological Syndrome of Lipid Nephrosis and Its Physiopathology, Pédiatrie 11:149, 1956.

19. Lange, K.; Craig, F.; Oberman, J.; Slobody, L.; Ogur, G., and LoCasto, F.: Changes in Serum Complement During the Course and Treat-

ment of Glomerulonephritis, A. M. A. Arch. Int. Med. 88:433, 1951.

20. Lange, K.; Slobody, L. B., and Strang, R. H.: Serum Complement Levels as a Guide for Diagnosis and Therapy of the Nephrotic Syndrome, J. Clin. Invest. 32:581, 1953.

21. Lange, K., and Wenk, E. J.: Investigations into the Site of Complement Loss in Acute Human and Experimental Glomerulonephritis and the Nephrotic Syndrome, A. M. A. Am. J. Dis. Child. 88:639, 1954.

22. Sadhu, D. P., and Mookerjea, S.: Studies on the Mechanism of Cholesterol Synthesis in Nephrosis, Metabolism 4:531, 1955.

23. Conn, J. W.; Vogel, W. C.; Louis, L. H., and Fajans, S. S.: Serum Cholesterol: Probable Precursor of Adrenal Cortical Hormones, J. Lab. & Clin. Med. 35:504, 1950.

24. Adlersberg, D.; Schaefer, L. E., and Dritch, R.: Effect of Cortisone, Adrenocorticotropic Hormone (ACTH), and Desoxycorticosterone Acetate (DOCA) on Serum Lipids, abstracted, J. Clin. Invest. 29:795, 1950.

25. Adlersberg, D.; Schaefer, L. E., and Drachman, S. R.: Studies on Hormonal Control of Serum Lipid Partition in Man, J. Clin. Endocrinol. 11:67, 1951.

26. Heppel, L. A.: The Electrolytes of Muscle and Liver in Potassium-Depleted Rats, Am. J. Physiol. 127:385, 1939.

27. Darrow, D. C.; Schwartz, R.; Iannucci, J. F., and Coville, F.: The Relation of Serum Bicarbonate Concentration to Muscle Composition, J. Clin. Invest. 27:198, 1948.

28. Moore, F. D.; Boling, E. A.; Ditmore, H. H., Jr.; Sicular, A.; Teterick, J. E.; Ellison, A. E.; Hoye, S. J., and Ball, M. R.: Body Sodium and Potassium: V. The Relationship of Alkalosis, Potassium Deficiency and Surgical Stress to Acute Hypokalemia in Man, Metabolism 4:379, 1955.

29. Danowski, T. S.: Respiratory Acidosis and Hypochloremic Alkalosis: Origins, Differentiation, Effects and Therapy, Diabetes 5:323, 1956.

30. Danowski, T. S.; Fergus, E. B., and Mateer, F. M.: The Low Salt Syndromes, Ann. Int. Med. 43:643, 1955.

31. Luetscher, J. A., Jr., and Johnson, B. B.: Chromatographic Separation of the Sodium-Retaining Corticoid from the Urine of Children with Nephrosis, Compared with Observations on Normal Children, J. Clin. Invest. 33:276, 1954.

32. Albrink, M. J.; Hald, P. M., and Man, E. B.: Water Content of Hyperlipemic Serum, abstracted, J. Clin. Invest. 33:914, 1954.

33. Sims, E. A. H.; Welt, L. G.; Orloff, J., and Needham, J. W.: Asymptomatic Hyponatremia in Pulmonary Tuberculosis, J. Clin. Invest. 29:1545, 1950.

34. Danowski, T. S.: Diabetes Mellitus with Emphasis on Children and Young Adults, Ch. 21, Baltimore, Williams & Wilkins, to be published.

35. Farnsworth, E. B.: Correlation of Excreted Compounds E and F with Clinical Course of a Nephrosis Patient Treated with ACTH and Compounds E and F, abstracted, J. Pharmacol. & Exper. Therap. 110:17, 1954.

36. Deane, H. W.; Shaw, J. H., and Greep, R. O.: Effect of Altered Sodium or Potassium Intake on Width and Cytochemistry of Zona Glomerulosa of Rat's Adrenal Cortex, Endocrinology 43:133, 1948.

37. Badinez, O., and Croxatto, H.: Modificationes histológicas de la corteza suprarrenal en la rata provocadas por la administración de cloruro de potasio y cloruro de sodio, Bol. Soc. biol. Santiago 5:40, 1948.

38. Jones, I. C., and Roby, C. C.: Some Aspects of Zonation and Function of the Adrenal Cortex: I. The Effects of Hypophysectomy on the Adrenal Cortex of the Adult Male Mouse, J. Endocrinol. 10:245, 1954.

Effect of Phenylalanine-Restricted Diet in Phenylketonuria II

F. A. HORNER, M.D.; C. W. STREAMER, M.D.; D. E. CLADER, M. A.; L. L. HASSELL, M.A.; E. L. BINKLEY Jr., M.D., and K. W. DUMARS Jr., M.D., Denver

In an earlier paper two of us (F. A. H. and C. W. S.) presented the short-term psychological and behavioral changes observed in two preschool phenylketonuric children treated with a phenylalanine-restricted diet.[1] In addition, a newborn sibling of one of the cases, who had received dietary treatment since 8 weeks of age, was reported as developing normally through the first 9 months of life. The present paper offers an additional year of follow-up on these three patients. It also reports on the changes observed in a second newborn and two 18-month-old children under long-term therapy.

Dietary Program

The phenylalanine-restricted diet used in this series is that outlined by Armstrong and Tyler.[2,3] Patients are given a phenylalanine-free diet consisting of a protein hydrolysate basal mix* (4.2 gm/kg/day), fat in the form of a vegetable oil (3.0 gm/kg/day) and CHO (10 gm/kg/day) for three weeks. On such a diet the serum phenylalanine level has been shown to return from abnormally high to normal levels. After the initial three-week period, phenylalanine, in the form of natural protein, is added to the diet in sufficient quantity to maintain the serum phenylalanine level between 3 and 5 mg/100 ml. (usually 3-8 gm. of protein a day).

Psychological Test Procedures

The tests used included the Gesell Behavior Inventory, the Merrill-Palmer Scale of Mental Tests, and the Stanford-Binet Form L. The tests were administered by two psychologists working alternately and independently of one another. As the older children developed more discriminating mental ability, more difficult tests were introduced.

Report of Cases

Case 1.—A 4¼-year-old boy apparently developed normally until age 6 months. At that time he sat alone. He did not stand until 14 months. At the age of 2 years, he was noted to show no interest in other children, did not play with toys, and showed no interest in feeding himself. He became progressively more restless, wild, and uncontrollable. At the age of 4 years, he presented as an attractive, ruddy-complexioned, red-haired, blue-eyed boy whose physical developmental pattern fell within the 75th percentile. He displayed tremendous hyperactivity, he had a very brief attention span, and his only vocalization was a continual hissing sound. Hyperactive deep tendon reflexes were the only positive findings elicited. The $FeCl_3$ test on the urine gave a green color, characteristic of phenylketonuria. His serum phenylalanine level was found to be 38 mg/100 ml. On Feb. 15, 1955, he was placed on a phenylalanine-restricted dietary regimen. The subsequent physical development of this patient, as well as the others, will be reported in detail in a subsequent paper. He has shown consistent increments in height and weight.

When first evaluated psychologically, at age 49 months, this boy showed extreme hyperactivity, no language, no social control, a D. Q. of 35 and a

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Department of Pediatrics and Division of Clinical Psychology, Department of Psychiatry, University of Colorado School of Medicine.

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* Merck & Co., Inc., Rahway, N. J., furnished the phenylalanine-free basal mix used in these studies.

D. A. of 18.† After the first 14 months of treatment, his D. Q. had increased to 69 and his D. A. was 44. Thus, in 14 months the increment of mental age was 26 months. After 22 months of treatment, he can play quietly, talk in meaningful sentences, and control his aggressive impulses most of the time. He is able to adjust well to a kindergarten class of normal children and is profiting from the experience.

Case 2.—This 4-year-old girl was noted to be retarded in the first year of life. She did not roll over until 1 year of age, sat alone shortly thereafter, and stood at 2 years. Convulsions were noted at 18 months. When seen at age 4 years she presented as an unmanageable child with reddish-blonde hair and brown eyes. Detailed examination was impossible, but a urine examination revealed a positive $FeCl_3$ test. The serum phenylalanine level was found to be 32 mg/100 ml. The patient has been on continuous dietary therapy since March 18, 1955, (age 4 2/3 years).

Before treatment she was extremely noisy, aggressive, hyperactive, and devoid of any meaningful language. Her D. Q. was 37, and her D. A. was 19. At 77 months, after 20 months of treatment, she still shows noticeable erratic behavior at times. However, she demonstrates greater social control, language development sufficient to allow easy communication with others, and a generally pleasing, friendly manner. Her D. Q. is 70 and her D. A. is 54. After 20 months of treatment she has gained 35 months' D. A.

Case 3.—A sibling of Case 2, born Feb. 4, 1955, was found to have phenylketonuria—as evidenced by a positive $FeCl_3$ urinary test at age 7 weeks. Previous serial urinary tests were negative. His serum phenylalanine level at 7 weeks was 55 mg/100 ml. One week later dietary treatment was initiated, and he has remained under dietary control to the present time.

Over-all development has been within normal limits. At age 2.5 months his D. Q. was 100, and at age 20 months his D. Q. is 91. He says single words, goes up and down stairs, and compares favorably in his developmental pattern with his older, unaffected brother.

Case 4.—A 17-month-old white girl was first seen in August, 1955, because of slowness in developing. She stood at 14 months of age. However, at 17 months she did not walk or speak understandable words and she showed only a constant erratic, purposeless activity. A maternal cousin was diagnosed as a Mongoloid, but otherwise the family history was negative. Pregnancy and birth were uneventful. Physical examination revealed a wild-appearing, blue-eyd, red-haired, fair-skinned child, weighing 10 kg. (22 lb.) and measuring 75.6 cm. (29¼ in.). The general physical examination was negative. Neurological examination showed hypotonic extremities. The urine was positive for phenylpyruvic acid, and the serum phenylalanine level was reported as 99 mg/100 ml. The patient's electroencephalogram was interpreted as normal. Following psychological evaluation, the child was placed on the above dietary regimen and has been on the diet continually since Nov. 16, 1955.

When first tested, at 20 months, she had a D. A. of 10.5 and a D. Q. of 52. She has demonstrated a steady growth in social responsiveness, controlled meaningful play behavior and beginning language development. The last test, after 11 months of treatment, showed a D. Q. of 73 and a D. A. of 22. In this period she has gained 14 months in mental age.

Case 5.—A girl born March 31, 1954, was the first child born to a 31-year-old, primagravida mother. Labor and pregnancy were uncomplicated. The neonatal and early months of life were unremarkable, except that the parents describe her as being "almost too good." At the age of 3 months she developed a severe and persistent diaper rash. At 6 months of age she was making no attempt to sit, roll over, smile, or coo. The parents noted that she seemed to be less active at this time than at 3 months. Her failure to look at objects raised the question of blindness. She was seen by an ophthalmologist who felt there was no defect in the visual apparatus. A pneumoencephalogram at 9 months of age showed evidence of cerebral dysgenesis. At the age of 11 months the diagnosis of phenylketonuria was established on the basis of a positive $FeCl_3$ urinary test. There was no history of convulsions or spasms, but the parents noted she seemed to be dazed at times in the months between diagnosis and treatment.

There is a history of a nervous breakdown in both grandfathers. Two half sisters are living and well and a younger full sister is also a phenylketonuric infant (Case 6).

The child was admitted to Denver Children's Hospital, and a phenylalanine-restricted diet was initiated Nov. 14, 1955. Examination at this time revealed a well-developed, fairly well nourished, placid, blond, blue-eyed white female infant weighing 10 kg. (22 lb.). The odor characteristic of phenylketonuric children was noted about her body. (This odor has been variously described as a sweet, pungent, or musty odor. It is not unlike the odor of certain commercial mydriatics, such as cyclopentolate [Cyclogyl] hydrochloride.) A marked diaper rash was present. Dentition was normal. The serum phenylalanine level was 54 mg/100 ml. Two EEG's prior to therapy revealed severe diffuse cortical disturbance, maximal in the anterior leads. Her present weight is 11.6 kg.

† D. Q., developmental quotient; D. A., developmental age.

(25½ lb.) and her height is 86.9 cm. (34 in.). A recent EEG, on Nov. 2, 1956, is within normal limits.

During 11 months of treatment this case has shown little change from her initial D. Q. of 42 to the resent D. Q. of 40. The only meaningful gain has been her starting to walk. She remains placid, listless, and expressionless, showing no new social skills or intelligent behavior.

CASE 6.—The infant sister of Case 5 was born April 26, 1956. Labor and delivery were uncomplicated. The infant showed some slight generalized cyanosis and was placed in oxygen for the first 24 hours of life. After birth, serial urine examinations for phenylketonuria and serum phenylalanine determinations were done.[4] Final confirmation of the diagnosis was made with a positive $FeCl_3$ test at 6 weeks. She was then placed on a phenylalanine-restricted diet. Repeated EEG's have all been within normal limits since initiation of diet. Her weight gain has been slow but steady.

She has shown development within normal limits since birth. The most recent evaluation gives a D. Q. of 100 and a D. A. of 7.5.

Comment

The observations presented herein on previously reported Cases 1 and 2 tend to confirm the accelerated mental development suggested in the preliminary report. Both children have changed from the severely mentally retarded state described by Jervis [5] to cooperative, friendly, rather attractive personalities. Case 4, age 20 months at the beginning of dietary control, was functioning at a slightly higher level initially and has also shown a sustained acceleration of her mental growth pattern. The results here are in accord with those earlier reported by Bickel and Gerrard,[6] Tyler and Armstrong, and Woolf, Griffiths, and Moncrieff.[7] Once improvement began in this group, the mental age advanced more rapidly than the chronological increments. The pronounced behavioral and psychological changes observed in these three patients were coincident with the dietary program that resulted in restoration of serum phenylalanine to normal limits.

Case 5, though initially similar to the above three children, has failed to demonstrate psychological changes. The dietary control has been good, as evidenced by maintenance of the serum phenylalanine level in the normal range. There are no other physical findings suggestive of a neuroectodermal defect, and the head is not microcephalic. The cerebral dysgenesis reported at 9 months of age may account for her failure to respond. The possibility of psychological factors acting to prevent improvement here is also being considered.

Cases 3 and 6 are among the earliest reported newborns with the disease.[8] They have now been under treatment for 21 and 7 months, respectively, and have followed a healthy developmental pattern as judged from their psychological evaluations. Case 3 did not develop a positive $FeCl_3$ urinary test until 6 weeks of age. The metabolic changes occurring in the newborn period have been documented by the report of Armstrong and Binkley, who showed in Case 6 that the serum phenylalanine level may be elevated for a considerable time before the abnormal metabolites are found in the urine. Urine examinations for phenylketonuria in the newborn period apparently may not give positive results before the age of 6 weeks.

In recent months we have had the opportunity to follow six phenylketonurics without diet control. Our observations tend to support the newer concept [9] that the mental retardation pattern in this disease may not be so severe as initially described by Jervis. The early reports of this condition were based on institutional studies and were necessarily weighted in favor of the more severely retarded children.

Because of this newer concept of mental function in untreated cases, the psychological improvement reported here conceivably could have been secondary to factors other than the restoration of serum phenylalanine to normal values. However, in none of the untreated patients we have observed has there been the sustained improvement in mental function reported above.

Summary

Six patients with phenylketonuria have been under treatment with phenylalanine-

restricted diets for periods varying from 8 to 22 months.

Two children who were not treated until the 5th year of life are showing sustained increments in their intellectual functioning. Of the two children treated in the 3rd year of life, one is showing marked acceleration in her developmental pattern while the second shows little significant change after 14 months of treatment. Two newborn infants treated since the appearance of phenylketonuria are following a healthy developmental pattern after 21 and 7 months, respectively.

It is suggested that on the basis of these observations the treatment of older phenylketonurics may prove valuable in some cases. The treatment of newborns with phenylketonuria may prevent the characteristic and profound mental changes often associated with this abnormality. It is suggested that negative urinary tests for phenylketonuria may be misleading during the neonatal period.

Marvin D. Armstrong, Ph.D., Laboratory for the Study of Hereditary and Metabolic Disorders, University of Utah College of Medicine, Salt Lake City, collaborated in this study by assisting in the preparation of diets and by performing the analytical determinations on blood and urine from the patients. This research was supported, in part, through a research grant from the United States Public Health Service.

7040 E. Fifth Ave.

REFERENCES

1. Horner, F. A., and Streamer, C. W.: Effect of a Phenylalanine-Restricted Diet on Patients with Phenylketonuria, J. A. M. A. 161:1628 (Aug. 25) 1956.

2. Tyler, F. H., and Armstrong, M. D.: Diseases of Nervous System: Metabolic Aspects of Some Neurological and Muscular Disorders, Ann. Rev. Med. 5:207, 1954.

3. Armstrong, M. D., and Tyler, F. H.: Studies on Phenylketonuria: I. Restricted Phenylalanine Intake in Phenylketonuria, J. Clin. Invest. 34:565 (April) 1955.

4. Armstrong, M. D., and Binkley, E. L.: Studies on Phenylketonuria: V., Proc. Soc. Exper. Biol. & Med. 93:418 (Dec.) 1956.

5. Jervis, G. A.: Phenylpyruvic Oligophrenia: Introductory Study of 50 Cases of Mental Deficiency Associated with Excretion of Phenylpyruvic Acid, Arch. Neur. & Psychiat. 38:944 (Nov.) 1937.

6. Bickel, H.; Gerrard, J., and Hickmans, E. M.: Influence of Phenylalanine Intake on Chemistry and Behaviour of a Phenylketonuric Child, Acta Paediat. 43:64 (Jan.) 1954.

7. Woolf, L. I.; Griffiths, R., and Moncrieff, A.: Treatment of Phenylketonuria with a Diet Low in Phenylalanine, Brit. M. J. 1:57 (Jan. 8) 1955.

8. Berendes, H.: Paper presented at Western Society for Pediatric Research, Fourth Annual Meeting, Salt Lake City, October, 1956.

9. Low, N. L.; Armstrong, M. D., and Carlisle, J. W.: Phenylketonuria: Two Unusual Cases, Lancet 2:917 (Nov. 3) 1956.

Persistent Common Atrioventricular Canal

Clinical and Pathologic Observations in Twelve Infants

SIDNEY FRIEDMAN, M.D., and RACHEL ASH, M.D., Philadelphia

Although the surgical treatment of persistent common atrioventricular canal has been successful in isolated instances, most attempts at correction of this complex congenital cardiac malformation have failed.[1-3] Surgical correction of this lesion involves the hazards of direct-vision intracardiac surgery carried out in conjunction with some system of extracorporeal circulation. Because there are many clinical features common to this anomaly and the more readily repaired isolated septal defects, the identification of this malformation and its differentiation from related congenital cardiac lesions is of practical importance. It seems pertinent, therefore, to report the clinical and pathologic findings in 12 uncomplicated instances of persistent common atrioventricular canal observed at The Children's Hospital.

The malformation consists of a common canal connecting the atria and ventricles (Fig. 1). A persistent ostium primum is combined with a defect in the upper portion of the ventricular septum. There is thus at this region free communication between the four chambers of the heart. In addition, there is malformation of the leaflets of the atrioventricular valve. The arrangement and number of the leaflets guarding this single atrioventricular orifice is variable. A frequent pattern is a set of four leaflets, including one large anterior and one large posterior leaflet, plus two small lateral leaflets. The anterior and posterior

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From the Department of Cardiology of The Children's Hospital of Philadelphia and the Department of Pediatrics, University of Pennsylvania School of Medicine.

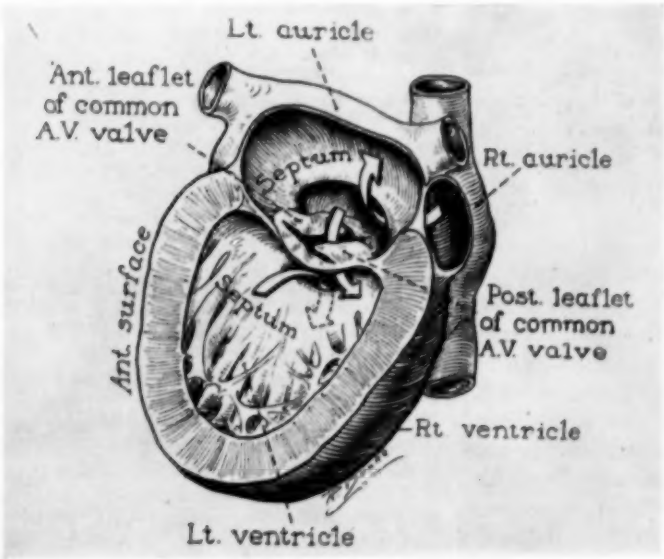


Fig. 1.—Common atrioventricular canal. The lateral walls of the left atrium and ventricle have been removed. The atrioventricular canal is common to both sides of the heart. It is guarded by a single valve possessing large anterior and posterior cusps, two right lateral cusps, and a left lateral one. The interatrial foramen primum is patent, as is the posterior upper portion of the interventricular septum. From Rogers, H. M., and Edwards, J. E.: *Am. Heart J.*, C. V. Mosby Company, 36:28, 1948.

leaflets override both ventricles, occupying a saddle-like position over the top of the ventricular septum. The normal septal cusps are absent, since their usual point of origin on the septum is missing. A variety of further distortions, fusions, and partial clefts in the leaflets is not uncommon. The chordae tendineae which arise from their margins may be attached to papillary muscle bundles or may insert on the upper margin of the muscular portion of the ventricular septum.

Most embryologists attribute this defective division to a failure of fusion of the anterior and posterior atrioventricular endocardial cushions. Associated with this failure in completion of the framework of tissue in the anteroposterior plane, there is a failure of both the atrial and ventricular septa to extend to the full limit of their normal growth. As a result, an associated defect is found in the inferior portion of the atrial septum and another in the superior portion of the ventricular septum. The atrial defect is in the position of the ostium primum while the ventricular defect involves in part the membranous portion of the ventricular septum.

The combination of anomalies mentioned above permits two major abnormalities in cardiac function. First, the septal defects permit shunting of large amounts of blood from one side of the heart to the other. The usual direction of the main portion of this shunt is from left to right. During certain phases of the cardiac cycle and under special circumstances, blood may flow from right to left through either of the septal defects or possibly from one ventricle to a contralateral atrium. Secondly, the abnormalities of structure and attachment of the leaflets of the atrioventricular valve permit some regurgitation of blood from ventricle to atrium during ventricular systole. Therefore, all chambers of the heart, especially the right-sided chambers, may be forced to work excessively, leading eventually to cardiac hypertrophy and dilatation. Death due to congestive failure, usually in the presence of intercurrent respiratory-tract infection, is a common terminal event in this condition.

In the extensive review of Rogers and Edwards,[4] the existence of partial or incomplete forms of this anomaly is noted. Specimens with defects in the atrial septum of the ostium primum variety associated with a simple cleft of the aortic cusp of the mitral valve are proposed as less severe or partial forms of persistent common atrioventricular canal. Blount[5] also mentions the possibility of gradations in the severity of this lesion in his recent report dealing with ostium primum defects. In the present communication, only the complete form of the malformation, not complicated by other lesions such as pulmonary stenosis, will be considered. However, the presence of an additional small atrial communication resulting either from a defect in the leaflet of the foramen ovale or incomplete closure of the foramen ovale will not be considered a complicating lesion, since it occurs so commonly and does not alter the basic cardiac dysfunction.

Methods and Materials

Clinical Data.—From the 11 cases in which this information was available, the average maternal age was found to be 32 years, with a range of 27 to 40 years. The average paternal age was 36 years, with a range of 28 to 47 years. The order of birth within each family of the 12 infants varied from the first to the 10th pregnancy. The obstetrical history in the 12 families was as follows: 7 families had only normal previous pregnancies resulting in healthy, living siblings; one family had no previous pregnancies; one family had two previous miscarriages; one family had a premature infant who did not survive, and 2 families had stillborns. The pregnancies which resulted in the 12 involved infants were all considered normal and uneventful, having been free of maternal illness. The weight at birth of the 12 infants varied from 2048 to 3413 gm.; 3 infants were less than 2500 gm.

Of the 12 infants there were 9 girls and 3 boys; 8 were white and 4 Negro. Eight of the twelve cases were Mongolian idiots; no other major noncardiac anomalies were present. The average age at the time of death was 8 months, with a range of 2 to 23 months. The two commonest complaints which precipitated hospitalization were failure to gain weight and/or some form of respiratory dis-

tress, usually tachypnea or dyspnea. The cause of death was congestive heart failure and/or intercurrent infection in all cases except one in which aspiration pneumonia was also thought to play a contributory role.

In 9 of the 12 infants a definite systolic murmur was present; in 3 cases no murmur was detected. There was considerable variation in the character and location of this murmur, but in at least six instances it was described as high-pitched, blowing, and apical. In the remaining cases, a left parasternal murmur was reported. In only one instance was a thrill palpated in association with a cardiac murmur. No diastolic murmurs were detected.

Pathological Data.—Pathological specimens were available to the authors for review in 8 of the 12 cases. Generalized cardiac enlargement was consistently found. The right ventricle was uniformly larger than the left ventricle, especially with regard to chamber size. This difference was less striking in comparing the thickness of the walls of the two ventricles. In all cases the cavity of the right atrium was between two and three times larger than that of the left atrium. The right-sided enlargement extended to the great vessels, the average circumference of the pulmonary artery being 2.8 cm. as compared with 2.2 cm. for the aorta.

It was extremely difficult to measure accurately the size of the ostium primum defect and/or the ventricular septal defect, since these are adjacent to each other and together form a single orifice between the two sides of the heart. In general, however, these two defects were found to be approximately equal in size, the atrial defect being slightly larger than the ventricular in four instances while the reverse situation was never found. In six of the eight specimens defects were found in the valve covering the foramen ovale. These varied in size from a diameter of 1.3 cm. to probe patency.

The leaflets of the atrioventricular valve varied widely in number and arrangement. The commonest pattern encountered was the presence of a large anterior and large posterior leaflet each of which extended from one side of the heart to the other, overriding the defect of the ventricular septum. Two lateral leaflets, one in each ventricle, were usually much smaller and gave rise to chordae tendineae which were attached to papillary muscles. The anterior and posterior leaflets were attached to the top of the ventricular septum by chordae tendineae and on their lateral aspects gave rise to chordae which were inserted in papillary muscle bundles. While it is difficult from examination of postmortem specimens to be certain of the competency of this common valve during life, it would certainly seem likely that some regurgitation of blood could occur during ventricular systole, especially after dilatation of the valve ring.

One cardiac specimen in the group demonstrated an interesting variation of embryologic significance. The membranous portion of the ventricular septum was defective as in the other specimens. However, as the large anterior and posterior leaflets passed from one side of the heart to the other across the plane of the two septa, they did not appear to lie above the ventricular septum in the usual fashion but were adherent on their atrial surfaces to the upper margin of the ostium primum defect. The adherent anterior and posterior leaflets failed to meet each other or fuse as they passed through the ostium primum defect, thus leaving a portion of the atrial defect still patent. Since the leaflets are derived from the atrioventricular endocardial cushion, this specimen represents, we believe, an

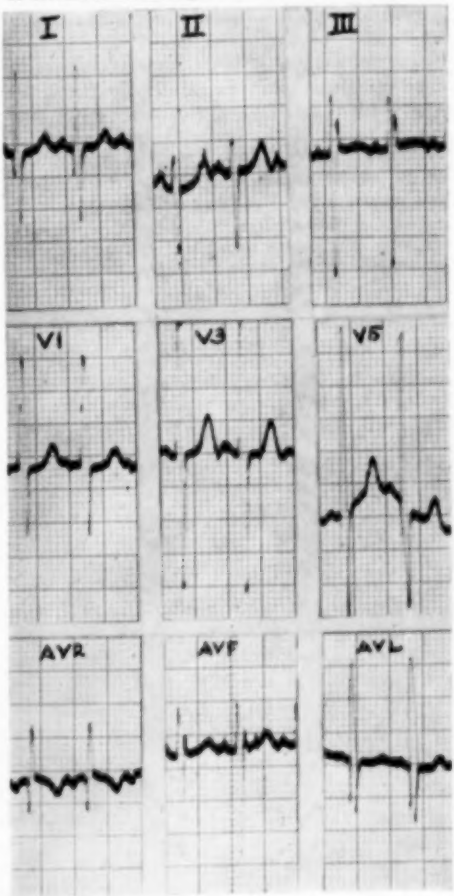


Fig. 2.—Electrocardiogram of a 6-week-old boy with persistent common atrioventricular canal. Tracing shows left-axis deviation with progressive increase in amplitude of S waves from Lead I to Lead III. Precordial leads demonstrate evidence of biventricular enlargement.

arrest in the developmental process at a stage of incomplete fusion rather than total failure of fusion of the atrioventricular endocardial cushions. Thus, the common atrioventricular canal in this specimen is almost but not completely divided into two separate orifices and, therefore, approaches the normal state.

Electrocardiograms.—One or more electrocardiograms were recorded in 6 of the 12 cases reviewed; in five instances precordial leads as well as limb leads were available for study. All six tracings were strikingly uniform and resemble closely the tracing of one patient, shown in Figure 2. A sinus tachycardia was present in all instances; no ectopic rhythms were noted. In only one case was the P-R interval prolonged; the Q-T interval was consistently within normal limits.

In all six cases, a marked left-axis deviation was present, varying from −70 to −100 degrees as measured by the triaxial reference system. The S waves were prominent in all limb leads, showing a progressive increase in amplitude from Lead I to Lead III. No abnormalities of the T waves or ST segments were observed. The P wave in Lead II was tall and peaked in all instances, varying in amplitude from 3.5 to 5.5 μv. In the precordial leads a tall R wave was consistently present over the right side of the chest; in two instances a prominent S wave was also present in this position. At the apex a high amplitude diphasic QRS complex was recorded in all cases. Thus, despite the left-axis deviation there was noted P wave configuration suggestive of right atrial enlargement and a QRS pattern in the precordial leads indicative of the presence of right ventricular or biventricular enlargement.

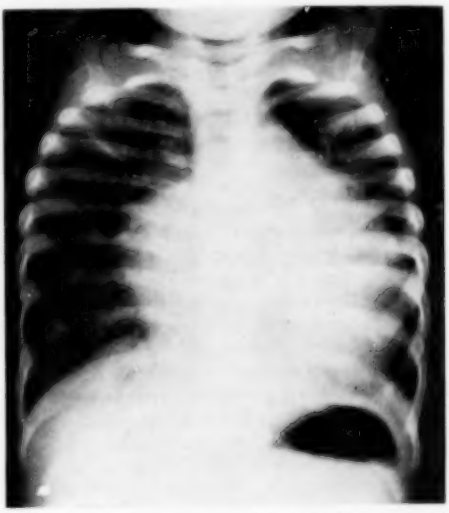
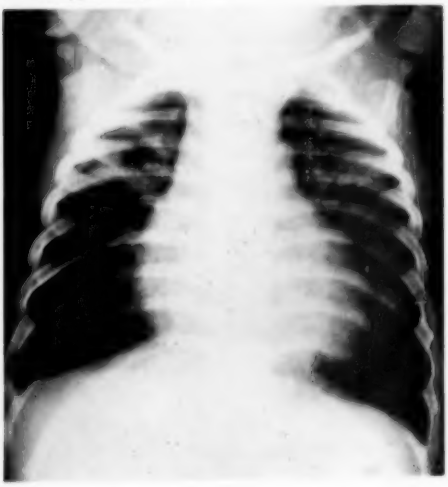


Fig. 4.—Roentgenogram of chest in 14-month-old girl who died 2 months later and was found to have persistent common atrioventricular canal. Film demonstrates massive cardiac enlargement, a narrow short superior mediastinal shadow and a prominent straight left upper arc which departs from the superior mediastinal shadow at a higher level than does the right-sided upper arc.

Fig. 3.—Roentgenogram of chest taken 2½ weeks prior to death in a 4-month-old Mongoloid infant with persistent common atrioventricular canal. The film shows only slight cardiac enlargement, a prominent pulmonary artery segment, and prominent pulmonary vascular markings, especially in the upper lung fields.



Roentgenographic Findings.—Roentgenograms taken in one or more positions were available for study in 11 of the 12 cases of persistent common atrioventricular canal. A moderate to marked degree of cardiac enlargement was present in all except one case in which only slight cardiac enlargement was noted. The chest film of the latter patient was taken approximately two months prior to death and is shown in Figure 3. In general, the roentgenographic findings were those conventionally observed in the presence of a large arteriovenous shunt. Right atrial enlargement was usually a prominent finding, as demonstrated by rounding and fullness of the right cardiac border in the anterior-posterior view and also by prominence of the anterior-superior cardiac border in the left anterior oblique view.

A convex or straightened left upper cardiac border was present in the anterior-posterior view in 7 of 11 cases. The marked fullness in this region was probably due primarily to dilatation of the main pulmonary artery and its left branch. The superior mediastinal shadow appeared to be both short and narrow in 6 of the 11 cases. This finding is probably related to the small size of the aortic arch plus the enlargement of the cardiac chambers and pulmonary artery in a cephalad

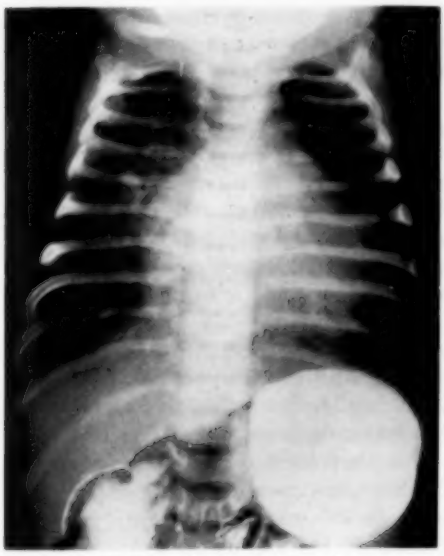


Fig. 5.—Roentgenogram of chest taken on same day of same patient as tracing in Figure 2. Moderate cardiac enlargement with the same general features of cardiac contour as in Figure 4 (another patient) are demonstrated.

direction. The left upper cardiac border in the region of the pulmonary segment joined the superior mediastinal shadow at a much higher level than the corresponding point of juncture made by the right-upper-heart border and the superior mediastinum (Figs. 4 and 5).

The films of all patients showed marked accentuation of the pulmonary vascular markings. The degree of engorgement varied directly with the degree of cardiac enlargement and appeared to be more intense in the upper than in the lower lung fields, especially on the right side. Overdistention or emphysema of both lung fields was present in 8 of the 11 cases.

Comment

In 1909 Keith [6] reported his findings in 14 pathologic specimens showing a persistent common atrioventricular canal. In each case a major complicating cardiac anomaly was present, and for this reason he postulated that this lesion never occurred unaccompanied by other cardiac malformations. Subsequent observations,[4,7] however, have demonstrated that associated major cardiac anomalies have been present in only approximately one-third of the reported cases of persistent common atrioventricular canal, the remainder occurring in an isolated form, such as in the 12 patients included in this report. Although there has been little uniformity among the associated cardiac lesions, certain of these have appeared more frequently than others. Recent reports [8,9] have pointed out the common association of pulmonary stenosis or atresia, dextrocardia, and biloculate heart with the persistence of a common atrioventricular canal.

Congenital anomalies of a noncardiac nature have also been noted to accompany this lesion with high frequency. Mongolism,[7,10-12] congenital absence of the spleen,[8,9,13] and varying degrees of malrotation [8,13] of the bowel are commonly mentioned in this connection. In the series of Rogers and Edwards [4] approximately one-third of the patients were Mongolian idiots. In our group of 12 patients the stigmata of Mongolism were the only major noncardiac anomalies found and were present in 8 cases. This relatively high incidence of Mongolism may be related somewhat to the fact that our material consisted entirely of patients dying early in life.

The oldest surviving patient in our group was 23 months at the time of death, the youngest, 2 months, and the average, 8 months. Among the 55 autopsied cases listed by Rogers and Edwards,[4] the average age of survival was 16 months, the median being 10 months; one-half succumbed in the first year of life. Rare persons with this lesion in an uncomplicated form are reported to attain advanced ages. The patient of Curtin [14] lived 58 years and was reported to be free of cardiac symptoms up until 1 or 2 years prior to death. The role of the complicating cardiac and noncardiac lesions in determining the survival time is apparently significant. The average survival time of persons with normal mentality in the 55 cases of Rogers and Edwards [4] was considerably longer than that of the Mongoloid children. In the same series it is also evident that those patients who survived longest had relatively few additional cardiac anomalies.

The findings on physical examination in patients with persistent common atrioventricular canal are not very helpful in making a precise anatomic diagnosis. Poor general somatic growth and development, cardiac enlargement, tachypnea, and/or dyspnea are findings common to patients with any large arteriovenous shunt. The character of the cardiac murmur may in some cases be of limited diagnostic assistance in suggesting the possibility of this complex malformation. In most patients a low-pitched parasternal systolic murmur is audible. In association with this, or sometimes as the only murmur, a high-pitched blowing systolic murmur, similar in quality to the murmur of mitral insufficiency of rheumatic origin, is heard at the apex or over the mid-precordium. Blount [5] and others [15] have attributed this high-pitched blowing murmur to regurgitation of blood through the incompetent atrioventricular valve during ventricular systole. Presumably the point of maximum intensity of the murmur depends upon the primary site of regurgitation. Thus, the murmur may appear to be loudest at either the apex or to the left of the lower sternum, depending upon whether the left or right side of the common atrioventricular canal permits the greater amount of regurgitation. In 3 of our 12 patients no murmur was audible at the time of examination, while only a single infant exhibited a thrill on palpation. In the report of Blount et al.[5] on defects in the atrial septum of the ostium primum type, two of which were probably associated with some deformity of the atrioventricular valve leaflets, it is interesting that at operation a jet of regurgitating blood could be palpated by the surgeon as it came through the orifice between the left ventricle and left atrium. At operation it was also possible for the surgeon to palpate a thrill over the posterior aspect of the right atrium despite the absence of a thrill over the chest wall.

The classical physical findings of congestive heart failure in infancy were present terminally in 11 of our 12 patients. Cyanosis is usually not a prominent clinical feature in patients with this lesion, except in terminal states. In those persons who survive long enough to develop occlusive pulmonary vascular changes and high resistance to pulmonary blood flow, a significant amount of reversal of shunt from right to left may occur and overt cyanosis may appear. Some right to left flow, detectable only by direct determination of arterial oxygen content and not evident to the clinical observer, is probably present in most patients with this lesion. The fact that all of our 12 patients died before the age of 2 years may account for the absence of prominent cyanosis prior to the terminal illness.

The electrocardiographic findings in this condition have received little mention in the past. In the case reported by Rogers and Rudolph [15] in 1953, an electrocardiographic tracing is presented which demonstrated marked left-axis deviation; no precordial leads were available in this patient. The tracing recorded from Ziegler's [16] patient with a common atrioventricular canal complicated by pulmonary stenosis also demonstrated left-axis deviation plus right ventricular preponderance in the chest leads. The tracing taken from Moragues' [17] patient similarly appears to show left-axis deviation. The book of Kjellberg et al.[18] presents a tracing with prominent progressively enlarging S waves in the limb leads of a patient with this lesion. The first two patients of Blount et al.,[5] who were reported to have an ostium primum defect plus deformity of the atrioventricular valve leaflets, clearly demonstrated left-axis deviation with S waves that became progressively larger from Leads I to III. It is extremely interesting that the third autopsied patient of Blount et al.[5] had two normal atrioventricular valves plus an isolated ostium primum defect and showed a completely right-sided type of electrocardiogram. This tracing was distinctly different from those observed in patients with persistent common atrioventricular canal and characteristic of those seen with large isolated atrial septal defects. One may conclude that the ostium

primum defect alone is not responsible for the paradoxical left-axis deviation. The latter seems to be related to deformity of the atrioventricular valve leaflets.

The six tracings available to us for study showed marked left-axis deviation, progressive increase in amplitude of S waves from Leads I to III, and a QRS pattern indicative of the presence of right ventricular preponderance or biventricular enlargement in the precordial leads. These findings have been consistently present in our experience with living patients in whom this diagnosis seems likely from clinical and catheterization studies. The finding of left-axis deviation is somewhat of a paradox in view of the predominantly right-sided cardiac enlargement observed in the pathologic specimens as well as in the precordial leads of the electrocardiograms and in the x-ray studies. Blount et al.[5] have suggested that this finding may be in some way related to the strain placed on the left side of the heart by the valvular insufficiency, presumably taking place predominantly on the left side. The severe anatomical distortions may provide a possible explanation for the left-axis deviation. The ridge of tissue which forms the normal anatomical location of the bundle of His is entirely missing in these specimens so that this conducting structure must follow an anomalous course. As a result, activation of the ventricular septum and subsequently of the two ventricles may possibly occur through an abnormal mechanism whose different orientation of electrical forces may reflect itself in the production of left-axis deviation and progressively taller S waves from Leads I to III.

Routine roentgenograms of the chest in patients with persistent common atrioventricular canal demonstrated only the nonspecific findings associated with a large arteriovenous shunt. Generalized cardiac enlargement, particularly of the right atrium and right ventricle, engorgement and dilatation of the main pulmonary artery and its major divisions, and generalized bilateral emphysema[19] of the lungs are changes which belong in this category. While no additional pathognomonic roentgenographic signs are recognized in this condition, the following were observed repeatedly in our series: (1) marked, rather than slight or moderate, cardiac enlargement, to both right and left of the midline; (2) a narrow and short superior mediastinal shadow which appeared to result from a cephalad enlargement of the cardiac chambers and great vessels plus an aorta of small size; (3) a prominent, relatively straight left upper arc in the anterior-posterior view which departs from the superior mediastinal shadow at a higher level than does the right-sided upper arc.

Gross cardiac enlargement was found at necropsy in 11 of the 12 patients included in this study. Taussig[20] has pointed out the not infrequent finding of a normal heart size in living patients with common atrioventricular canal prior to the onset of cardiac symptoms and congestive failure. One patient in our group (Fig. 3) showed only slight cardiac enlargement at the age of 3 months, death occurring 2 months later. Thus, it appears that gross cardiac enlargement is not invariably present in the absence of cardiac symptoms or signs of congestive failure.

In the presence of a large left-to-right shunt, relatively little specific diagnostic aid would be anticipated from angiocardiography. In the patient of Gasul[21] a peripheral venous angiocardiogram carried out at the age of one month showed immediate opacification of all four cardiac chambers as well as the two great vessels with persistence of the contrast media within the heart for a period of at least 10 seconds as a result of reopacification. The four cases of Abrams and Kaplan[22] demonstrated the same findings. The findings of selective angiocardiography in one case are described by Kjellberg et al.[18] In none of the 12 patients in this series was this study carried out.

Few reports of the results of right-heart catheterization in confirmed cases of persistent common atrioventricular canal are

available.[1,5,18] These demonstrate a progressive, stepwise increase in oxygen content in samples removed from the right atrium and right ventricle, indicating the presence of a left-to-right shunt at both atrial and ventricular levels. In some cases the atrial shunt has been greater; in others, the ventricular. The right ventricular and pulmonary artery pressures have varied from normal to hypertensive levels, depending apparently upon the size of the ventricular septal defect, the amount of pulmonary blood flow, and the presence of occlusive changes within the pulmonary arterioles. Peripheral arterial unsaturation, usually of a mild degree, is also a common finding. The presence of a common central defect to which all four cardiac chambers have access plus associated pulmonary hypertensions makes the possibility of a right-to-left shunt readily understandable.

Some diagnostic assistance may also be derived from observation of the course and action of the catheter within the heart during catheterization. The catheter may be seen to pass readily from the right atrium into the left atrium and almost immediately into the left ventricle. Passage into the aorta is unlikely, since the catheter tip is directed in a caudad direction toward the cardiac apex. On withdrawal the catheter may be seen to move rapidly from the left ventricle back into the right atrium not remaining in the left atrium for any significant period of time. Kjellberg et al.[18] have described a case in which the catheter returned to the right ventricle from the left ventricle through a ventricular septal defect. Dye-dilution curves in patients with persistent common atrioventricular canal have also been reported recently.[23]

The diagnosis of persistent common atrioventricular canal may frequently be suspected from a review of the clinical history, physical examination, routine roentgenograms, and the electrocardiogram. In our own experience the electrocardiogram has been most useful in directing attention to this diagnostic possibility. While all of the instances of this lesion encountered by us have demonstrated a left-axis deviation with progressive increase in amplitude of the S waves from Lead I to Lead III and the QRS pattern of right or biventricular enlargement in the precordial leads, it is well to point out that not all patients with these electrocardiographic abnormalities have this malformation. We have seen these findings in a patient presumed to have an isolated congenital malformation of the mitral valve, and in patients with various partial forms of the lesion under consideration.

From the surgical point of view the differentiation of these patients from those with large isolated atrial septal defects with or without anomalous pulmonary venous drainage is important, especially in view of the possible similarity in catheterization findings. The high-pitched apical systolic blowing murmur present in some patients with persistent common atrioventricular canal is one useful guide in differentiating this lesion from uncomplicated septal defects. In contrast, the murmur usually associated with an isolated atrial defect is low-pitched and best heard in the second left interspace. An electrocardiogram with left-axis deviation occurring in a patient with clinical and physiologic evidence of an atrial septal defect should also be taken as a strong warning of the possible complicated nature of the lesion. The differentiation of large isolated ventricular septal defects from the lesion under consideration can at times probably not be made with certainty by conventional clinical or physiologic studies. The finding of a significant rise in oxygen content in the right atrium as well as in the right ventricle is evidence for the more complex lesion. Finally, if surgical correction of persistent common atrioventricular canal is undertaken, repair of the additional atrial septal defect in the region of the foramen ovale must not be overlooked.

Summary

The clinical, laboratory, and gross pathologic findings in 12 uncomplicated cases of

persistent common atrioventricular canal are reviewed.

The usefulness of the electrocardiogram as an aid in the diagnosis of persistent common atrioventricular canal is emphasized. All of the electrocardiograms available for study in these patients were strikingly uniform, demonstrating (1) a left-axis deviation with progressively increased amplitude of S waves from Leads I to III and (2) evidence in the precordial leads of either right ventricular preponderance or biventricular enlargement.

A high-pitched apical systolic blowing murmur in the lower precordial or apical region is heard frequently in the presence of this lesion and may also be of limited diagnostic assistance.

Dr. Bernice Wedum assisted in the interpretation of the pathologic specimens, and Dr. Irving J. Wolman made available the pathological material studied.

18th and Bainbridge Streets (46).

Addendum

Attention should be directed to a symposium on the subject of persistent common atrioventricular canal published in the Proceedings of the Staff Meetings of the Mayo Clinic (31:487-529, 1956) shortly after the present manuscript was completed for publication.

REFERENCES

1. Varco, R. L.: Direct Vision Intracardiac Surgery for Certain Congenital Malformations: Cross Circulation-Oxygenator Techniques, Problems, and Accomplishments, Tr. & Stud. Coll. Physicians Philadelphia 24:45, 1956.

2. Muller, W. H., Jr.; Smith, S. W.; Dammann, J. F., Jr.; Adams, F. H., and Darsie, M. L.: Considerations and Physiologic Studies in the Closure of Interauricular Septal Defects, Surgery 37:1, 1955.

3. Lewis, F. J.; Taufic, M.; Varco, R. L., and Niazi, S.: The Surgical Anatomy of Atrial Septal Defects: Experiences with Repair Under Direct Vision, Ann. Surg. 142:401, 1955.

4. Rogers, H. M., and Edwards, J. E.: Incomplete Division of the Atrioventricular Canal with Patent Interatrial Foramen Primum (Persistent Common Atrioventricular Ostium): Report of 5 Cases and Review of Literature, Am. Heart J. 36:28, 1948.

5. Blount, S. G.; Balchum, O. J., and Gensini, G.: The Persistent Ostium Primum Atrial Septal Defect, Circulation 13:499, 1956.

6. Keith, A.: Malformations of the Heart, Lancet 2:433, 1909.

7. Meeker, L. H.: Congenital Defect of Heart in a Mongolism Idiot, J. Tech. Methods 14:72, 1935.

8. Polhemus, D. W., and Schafer, W. B.: Congenital Absence of the Spleen: Syndrome with Atrioventricularis and Situs Inversus: Case Reports and Review of the Literature, Pediatrics 9:696, 1952.

9. Bush, J. A., and Ainger, L. E.: Congenital Absence of the Spleen with Congemtal Heart Disease: Report of a Case with Ante Mortem Diagnosis on the Basis of Hematologic Morphology, Pediatrics 15:93, 1955.

10. Robinson, D. W.: Persistent Common Atrioventricular Ostium in a Child with Mongolism, Arch. Path. 32:117, 1941.

11. Goetsch, C.: Persistent Ostium Atrio-Ventriculare Commune with Bacterial Endocarditis in a Mongolian Idiot, J. Tech. Methods 18:117, 1938.

12. Hambach, R.: Ein Beitrag zur Frage der Kombination von Habitus mongoloides mit angeborenen Herzmissbildungen, Ann. Pediat. 183:77, 1954.

13. Baumann, J.: Agenesie der Milz, Herz- und Gefässmissbildungen und Situs inversus partialis—ein charakteristischer Symptomenkomplex, Helvet. pediat. acta 9:199, 1954.

14. Curtin, J. Q.: Congenital Cardiac Anomaly: Persistent Common Atrioventricular Ostium, Am. Heart J. 44:884, 1952.

15. Rogers, H. M., and Rudolph, C. C.: Persistent Common Atrioventricular Canal, Am. Heart J. 45:623, 1953.

16. Ziegler, R. F.: Some Aspects of Electrocardiography in Infants and Children with Congenital Heart Disease, Dis. Chest 25:490, 1954.

17. Moragues, V.: Persistent Common Atrioventricular Ostium, Am. Heart J. 25:123, 1943.

18. Kjellberg, S. R.; Mannheimer, E.; Rudhe, U., and Jonsson, B.: Diagnosis of Congenital Heart Disease, Chicago, Year Book Publishers, Inc., 1955.

19. Krabbenhoft, K. L., and Evans, W. A., Jr.: Some Pulmonary Changes Associated with Intracardiac Septal Defects in Infancy, Radiology 63:498, 1954.

20. Taussig, H. B.: Congenital Malformations of the Heart, London, The Commonwealth Fund, Division of Publications, 1947.

21. Gasul, B. M.; Weiss, H.; Fell, E. H.; Dillon, R. F.; Fisher, D. L., and Marienfeld, C. J.: Angiocardiography in Congenital Heart Disease Correlated with Clinical and Autopsy Findings: 5 Year Clinical and Pathological Study of 34 Cases in Infants and Young Children out of Series of 1100 Patients, and 425 Angiocardiograms, A. M. A. Am. J. Dis. Child. 85:404, 1953.

22. Abrams, H. L., and Kaplan, H. S.: Angiocardiographic Interpretation in Congenital Heart Disease, Springfield, Ill., Charles C Thomas, Publisher, 1956, p. 161.

23. Swan, H. J. C.; Hetzel, P. S.; Burchell, H. B., and Wood, E. H.: Relative Contribution of Blood from Each Lung to the Left-to-Right Shunt in Atrial Septal Defects, Circulation 14:200, 1956.

Parents' Emotional Response to Child's Hospitalization

HELEN GOFMAN, M.D.; WILMA BUCKMAN, M.S.W., and GEORGE H. SCHADE, M.D., San Francisco

A number of studies[1-3,5] have emphasized the need for programs of hospital care to take into treatment consideration the interdependence of the child's psyche and soma in the promotion of recovery and prevention of unnecessary physical and mental sequelae. In addition, there are data[6,7,9] to confirm the vital need of a supportive parent-child relationship, not only to promote healthy growth and development of the child but also to sustain the child during times of great stress—as in the experience of illness and hospitalization.

When a child becomes ill, a change usually takes place in the parent-child relationship.[4,8] The parents become more protective and indulgent; the child, at the same time, becomes more dependent on his parents and more demanding of their presence and attention. If the illness necessitates hospitalization, this entails separation of parent and child and relinquishment of the child's care, usually to strange physicians and nurses, at a time when parent and child have an increased need for each other.

Our initial study[5] was concerned with the child's emotional response to this experience and revealed many areas in which the physician could do much to reduce the emotional trauma associated with hospitalization. Recognizing that this experience is also difficult for parents, we conducted a further study to determine where physicians might be of more help to the parents as well as to their hospitalized children.

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From the Pediatric Mental Health Unit, University of California Medical Center.

Method

One hundred parents were interviewed at the time of the child's hospital admission and sixty-eight parents were interviewed on discharge of their child for the purpose of ascertaining their reactions to admission, hospitalization, and discharge, as well as their own and their child's preparation, their feelings and understanding about his illness.

Admission

It was explained to these parents on admission of their child that, in an attempt to be of more help to them and their child, we were interested in how they felt about bringing their child to the hospital. The following questions were asked:

1. *We know it isn't easy for a parent to bring his child to the hospital. How did you feel about bringing your child to the hospital today?*

Of the 100 parents interviewed on the child's admission, all expressed anxiety regarding separation from their child—in 57, this anxiety was overwhelming. They had a dread of leaving the child and a fear that understanding care would not be given. The following are some examples of responses of these parents:

It broke my heart to leave Jimmy; we're so used to each other—he's so used to me, he won't eat for anyone else.

I feel terrible. He's always been with me. I know he'll get good care, but he'll be lonely. He doesn't want me to go away. He wants me to stay. I'd like to stay all the time.

I'm worried about the kind of care he will get, what they will do to him, if he will be happy, and what kind of food they will feed him.

The 43 less anxious parents expressed relief that the hospital was available for their child's care and hoped for a diagnosis and cure.

I hope they can find something to cure him. I want to have a well and normal boy, able to play with other kids.

It's wonderful to have this facility. I hope they can find the cause and some treatment, rather than having her stay at home and get worse.

A tremendous psychological impact on the parents is associated with the hospitalization of their child. Over one-half of these parents wept and had such difficulty in coping with their own fears and anxieties that they were unable to give support to their child at the time of his great need and stress. It is in this area that many parents showed a need for help. Because we recognized that a common basis for anxiety is fear of the unknown, we attempted to determine these "unknowns." Our next question, therefore, referred to the preparation for hospitalization of the parents and the child.

2. What did your doctor tell you or your child about where he was going, why, or anything about the hospital?

Seventy-six of the parents were told only that their child was entering the hospital for more tests, or that the hospital had "better equipment" or the "newest facilities," but without any explanation of the tests, the equipment, the facilities, or the hospital set-up. All allowed enough time for preparation and explanation except for one admission of an urgent emergency nature.

The doctor only told me the name of the hospital and that there would be tests and from that they would determine treatment. He didn't tell us anything about the tests or the hospital—the waiting, that we would talk to several doctors, or that I would need a deposit. It would have helped.

The doctor said it would be easier to examine him here. I didn't know what he meant.

The physicians of only 24 of the parents had explained to them and to their child why the child was being hospitalized and what they could expect in the way of tests and ward set-up. These parents did not seem as fearful regarding the separation and their child's hospital stay.

To determine how parents themselves prepare their children for hospitalization, we asked the following question:

3. What did you tell your child to explain why you were bringing him today?

Forty-seven of the parents had made some attempt to prepare their child for hospitalization. The following are some of the samples of varying attempts:

I told him we were going to see a doctor at the hospital.

To see why the kidney doesn't work—so doctors can get you well.

We told him since he couldn't play outside in the cold, that the doctors would fix him so he could, that he would eat off a big tray and be with other children.

Fifty-three of the parents did not inform their children that they were going to leave them in the hospital. Thirty-eight of these felt the child was too young to understand (some of these children were infants, but sixteen were between 3 and 4 years of age); the other fifteen parents did not realize that it was important or were afraid to tell their child and had tricked him into coming:

We told her we were taking her for a ride. We were taking her to see some children and stuff like that, to see some babies and play with some toys.

I told her nothing—just going for a bus ride—a vacation, just to see the doctor.

We were afraid to; no, I didn't—I just snuck off. When he changed clothes here, he knew what would happen.

I didn't—he knows he has heart trouble—I let him put two and two together. He's eleven.

These parents were most anxious regarding separation. Their anxiety was greatly relieved if they were given an explanation of the ward set-up and visiting hours, so that before they left they could prepare their child as to what to expect.

These parents expressed a desire to know the routine on a children's ward: Would their child be in bed all the time in a room by himself, lonely and isolated? Would the hospital do anything to amuse or distract him? When and how often would they be able to see him? Could he have any of his own favorite possessions? Would the nurses comfort him if he were in distress or would they just let him cry?

Many out-of-town parents said, "We could have brought his new cowboy hat that he loves so!" or

If I'd only known, we could have brought his own robe and slippers. He wanted to bring them, but I didn't think it would have been allowed.

If I could have told him he'd be with other boys his age he would not have worried so about coming.

If I had known you had a school teacher here who sees the children every day, Tom wouldn't have spent all these weeks worrying about getting behind in school while here.

We found that many parents not only wanted information and time to prepare their child for hospitalization but also wanted the physician to help in this preparation. One mother had brought her 3-year-old son to the clinic for a post-tonsilloadenectomy check for which she prepared him and was suddenly informed that he must be hospitalized for bronchopneumonia. She complained, "The first time I brought him here for a tonsilloadenectomy it was explained to him and I had time to prepare him. This time I'm not so pleased—the doctor didn't say anything to my child about coming into the hospital. The first chance I had I told him he was going, but I didn't have enough time before they took him away to really explain. I can hear him crying and calling for me." When asked how she felt when the physician didn't say anything to her child, she said, "I felt neglected and left out."

Thus, we found that preparation of the parent and child for what to expect was an important factor in diminishing separation anxiety. Parents expressed a desire to know why hospitalization for their child was necessary in the particular hospital to which he was sent, what to expect in the way of hospital facilities for their comfort as well as help in preparing their child, and—where possible—what procedures would be necessary and the risk involved.

Another source for parental anxiety was the fear regarding their child's illness. To determine these fears we asked this next question:

4. *We know it is difficult to have a sick child. What bothers you most about his illness?*

Forty-seven of the parents expressed fear of the unknown as being the most bewildering factor—not knowing what was wrong with their child or what was going to happen to him. For example,

Not knowing what is really the trouble. If I knew how serious it was, I'd know more or less where I stand. It's the unsureness that bothers me.

Not knowing his future possibilities. I have a terrible feeling of helplessness when he has attacks. It is the ignorance of the situation that bothers me.

Thirty-three of the parents were fearful that their child might be "this way" all his life. They worried about the child's future and how they could help him face and live with his chronic illness.

The fact that this can be a chronic illness and could be serious. I don't want her to live with this all her life. She's a little girl. She wants to grow up and have babies.

The future, how can he have a family and support them? How can he go on with one lung out? I fear I will lose her, that there is no cure for it.

Thirteen parents feared their child had an incurable, fatal disease. The remaining seven parents stated that their greatest difficulty was leaving their child in the hospital.

Modification of Admission Procedure

As our study progressed we became aware that another important factor in the parents' separation anxiety was our own admission procedure, which involved immediate separation of the child from his parents on entry to the pediatric ward. The child, often screaming and struggling, was taken by the nurse to be undressed, weighed, measured, "temperatured," and placed in bed in an isolation unit. The parents were escorted to a nearby waiting room to wait for the physician to appear for history taking. Meanwhile, they could hear their child crying and calling for them but could not see him and did not know where he was. Their anxiety was often at high pitch by and during the time the physician took the child's history.

UNIVERSITY OF CALIFORNIA HOSPITALS
PERSONAL RECORD FOR CHILDREN UNDER TWO YEARS

Name _____ Child's birthdate _____

Does the child have a nickname _____ If so, what is it _____

Parent's name _____

Parent's address while child is in the hospital _____
Telephone number where parents can be contacted _____

Child's religion _____ Has child been baptized _____

EATING HABITS
Is child breast fed _____ Use bottle _____ Spoon _____ Cup _____

Does he feed himself _____

Is he held for feedings _____ How many feedings in 24 hours _____

Is child fed when hungry _____ If on schedule - at what hours _____

Present diet _____
Is child allergic to foods: List them _____

What is present formula _____

Will he take water and fruit juices _____ What kind of juices _____

How _____ By bottle _____ By cup _____

Is he toilet trained _____

Does he use a toilet chair or toilet _____

What is the word used for urination _____ Bowel movement _____

Does he sleep well _____ Take a nap _____ What time _____

What kind of toy does he like _____ Any favorite toy _____

Has he been cared for by persons unfamiliar to him _____

Do parents plan to visit child _____ If so, when _____

VISITING HOURS: Week days 1:30 - 2:15 and 4:30 - 7:00 Sundays and holidays 1:30 - 7:00

Hospital telephone number: MO - 4-3600 Extension _____

The doctors are available to talk to you during visiting hours. You may call by telephone at any time if you cannot visit. You may call between 1:30 and 2:30 in addition.

Your doctors are _____ and _____
Your head nurses are _____ and _____

Visitors of children patients must be at least sixteen years of age.
Candy or food may be brought in to the children only with the consent of the head nurse.

Figure 1A

With the cooperation of the medical and nursing staff, the admission procedure was modified to allow for a more gradual separation of the child from his parents after both had become acquainted with the ward personnel and facilities. The purpose of this modification was to show the child (and his parents) that the personnel who would care for him were people whom his parents knew and could trust.

On admission now the nurse who is assigned to the care of the child is introduced to the child and his parents, accompanies them to the room (children are no longer routinely isolated) which the child will share with other children of his own age. The nurse acquaints him with the room and his roommates and assists the parents in putting him in bed. The parents are encouraged to stay with the child until the physician is available for history taking. During this time the nurse fills out the questionnaire, as shown in either Figure 1*A* or Figure 1*B*, which in addition to

UNIVERSITY OF CALIFORNIA HOSPITALS
PERSONAL SHEET

Name _____ Child's birthdate _____

Parent's name _____

Parent's address while child is in the hospital _____
Telephone number where parents can be contacted _____
Child's religion _____ Had child been baptized _____
Does he have a nickname _____
Are there other children in the family? _____ Brothers _____ Age _____
Sisters _____ Age _____

EATING HABITS
How is he usually fed? Bottle _____ Cup _____ Spoon _____ Feeds self alone _____
Feeds self with help? _____ Foods disliked _____
Is child allergic to any foods _____

ELIMINATION
Is he toilet trained _____ How long _____ Does he wear diapers _____
What is the word for urination _____ Bowel movement _____
Is child taken to the toilet at night _____ If so, at what time _____

SLEEPING HABITS
Does he sleep well _____ Does he take a nap _____ When is bedtime _____
Does he sleep alone _____ Bed with sides _____ Adult bed _____
Does child have a special bedtime routine _____ If so, what is it _____
_____

PLAY
What kind of play does he enjoy _____
Is he used to playing alone _____ With other children _____
With adults _____
Does he have a pet at home _____ What is it _____

SCHOOL
Does child enjoy school _____ Grade _____ Name of school _____

PERSONAL HABITS
Does he dress himself _____ With help _____ Wash his face _____
Comb his hair _____ Brush his own teeth _____
Why does he think he is being admitted to the hospital _____
Has he ever been in a hospital before _____
Doe he have a fear of unfamiliar adults _____ Doctors and nurses _____
Do parents plan to visit child _____ If so, when _____

VISITING HOURS: Week days: 1:30 - 2:15 and 4:30 - 7:00. Sundays and Holidays - 1:30 - 7:00
Hospital Telephone number: MO - 4-3600 Extension _____

The doctors are available to talk to you during visiting hours. You may call by telephone at any time if you cannot visit. You may call between 1:30 - 2:30, in addition.

Your doctors are _____ and _____
Your head nurses are _____ and _____

Visitors of children patients must be at leas sixteen years of age.
Candy or food may be brought in to children only with the consent of the head nurse.

Figure 1B

providing valuable information for the care of the child also gives the parents a feeling "that you are interested in my child as a person, that you are interested in his being happy and comfortable as possible." The physician, when he is available, introduces himself and explains to the child that he must talk to the parents but that the parents will return before they leave.

With this modification in admission procedure, visiting hours have been extended from 1:30-2:30 p. m. daily to 1:30-3:15 p. m. and 4:30-7:00 p. m. daily (1:30-7:00 week-ends and holidays). Some of the nursing and house staff were skeptical about this extension, but the results have been so gratifying that they now request a further extension of visiting hours.

With the institution of a more gradual parent-child separation and relaxation of visiting hours, we have observed a decrease in the degree of separation anxiety on admission as well as after visiting hours.

Hospital Routine

To determine parents' reactions to hospital routine and to discharge procedures, 68 parents were interviewed on their child's discharge after a talk with the physicians who had cared for their child in the hospital.

The first two questions which were asked related to the parents' feelings about the hospital stay:

1. *How do you feel now about the hospital as compared with the way you felt when you first brought your child to the hospital? If different, why?*

Forty-four of the parents felt better about the hospitalization of their child. Twice as many of these parents felt better about the hospital because of the friendly, personal handling of their child by the hospital staff as compared with those parents who felt better because of the diagonstic studies and treatment. Of the 24 parents whose attitude did not change, 18 volunteered the importance to them of their child's personal care by the nurses and doctors.

> We were relieved when we visited to see him happy and content—of course, he wanted to go home. We noticed how the other children felt about the nurses, how they seemed at home and content. You can learn much by a child's actions; they're honest about how they've been treated. The nurses were kind like mothers would be to children.

The importance of personal handling of the child as compared with his medical treatment may be a surprise, but personal handling is important to the parents in evaluating us as physicians and nurses. Without this consideration of their child, his medical care and the best diagnostic studies and treatment would lose much of their meaning for them.

2. *When during your child's stay at the hospital were you most upset? When was your child most upset? How did you handle it? When and how could we have been of more help to him or to you?*

Twenty-nine of the parents were most upset at admission, when they left their child and feared what would happen to him. They emphasized the help at this time of a warm and friendly staff to their child and to them. One mother, whose child had been on our ward several times previously and after our revision of admission and visiting hours, said,

> I look over the nurses and if they seem nice and are good to me I feel relieved. Then I can leave my baby better. Being allowed to stay with them and help put them to bed, instead of being chased out prematurely, is so much better.

Thirty-nine of the parents were most upset:

(a) Before important procedures or after surgery (9). All these parents emphasized the need for preparation and support from the staff at this time. If these procedures were not explained, many parents worried needlessly. The following is given as an example.

> The parents of a 7½-year-old boy with Banti's syndrome said they were most upset "when they took bone marrow from Tommy and we didn't know why. There was a patient in the same room who had leukemia and his parents said that's how it was diagnosed. We were afraid for hours until they explained that this was for a different reason." Yet, later, their child underwent very long and serious surgery. These parents withstood this experience well because, as they explained, "When he was in surgery, some of the doctors passing through the waiting room who had never seen us before were thoughtful enough to tell us things were going well. And our own doctor was wonderful; he kept us informed all the way."

This emphasizes that the preparation so important for hospitalization must be a continuing process throughout the hospital stay —by preparing the parents and the child for each procedure and by appreciating their accompanying anxieties.

(b) On admission, when the parents were fearful of "what the doctors would find was wrong with their child"(6).

(c) When they had to leave at the end of visiting hours (5). These parents empha-

sized their appreciation of the help given to them by the nurses and physicians in comforting and distracting their child at this time.

(d) When they received an unfavorable diagnosis (4). All these parents felt a need for more time to talk to the physician.

(e) On finding something unexpected about their child on visiting (6); for example,

"finding he had a cold we didn't know anything about"

"finding they had shaved part of his hair for a transfusion"

"seeing the child tied down for a urine specimen"

It is helpful if the staff can prepare the parents and not allow them to discover the change in their child themselves, to avert the resultant apprehension and antagonism which these discoveries engender.

(f) When their child had to stay longer than they expected (4).

(g) Five were most upset after surgical procedures; when they telephoned and got no information; when they saw other parents crying; when their child seemed indifferent to them when they came to take him home; when they signed the operating permit.

We found that the child's greatest upset corresponded to that of the parents. Nineteen of the children were most upset when they were left on admission, six after serious procedures or surgery, five at the end of visiting hours; two were most upset when they had to stay in the hospital longer than they had expected.*

Many parents, in discussing their reaction to hospital routine, emphasized the importance of the staff's attitude to them as parents. One mother whose 3-year-old child had been on our ward several times since birth said, with much feeling,

I used to feel like they didn't want parents around—that we were a waste of time or in the way. They wouldn't let me feed her, and if I changed her diaper they acted as though I had sinned. Now it is so much better; they even encourage me to feed her when I visit. There is nothing so bad as inactivity when you have a sick child.

Discharge

The following questions were asked as an aid in evaluating our discharge procedures:

1. *Did your doctor explain to you the tests done on your child? Do you have any suggestions as to how we can help you and your child when tests are to be done?*

Forty-nine of the parents felt the physician had explained everything sufficiently. Nineteen of the parents felt the physician had not given them an adequate explanation because he was too busy or rushed or because of his use of medical terms which they did not understand.

The almost universal suggestion from parents was the importance of preparation of the child by the staff for procedures, in order to reduce his fear and improve cooperation. One mother said, "Even with little kids, if they know what's going to happen, it helps."

2. *Do you feel the doctor gave you all the information about your child's illness which you wanted to know? If not, why were you unable to get this information?*

Fifty-four of the parents felt they had received the desired information. Many of them stated they had never had a physician who spent so much time with them or answered their questions so well. The remaining 14 parents felt they had not received the desired information because the physician was too rushed or because he used complex terms which they did not understand.

One father said,

It was a little like pulling teeth to get a chance to ask all our questions. So much time was taken when we were admitted and in a relaxed situation talking with many doctors. Now, after the tests are taken and we, as parents, would like a chance to ask questions, then everyone is too busy. We did get all the information, but it was sure hard to get."

* Of the 68 parents interviewed, 36 were parents of children who were too young to say when they felt most upset.

3. *Did you feel you received the information necessary for the further care of your child at home?*

Eighteen of the parents felt they had not received the necessary information. Their reasons fell into three categories:

"The doctor was too rushed."

"We were so excited taking our child home we forgot to ask questions."

"We were too upset by the diagnosis to listen."

Several of these parents volunteered that they would appreciate written instructions to which they could refer at home.

Since about one-third of the parents who were interviewed expressed some inadequacy in the discharge procedures, this has also been modified so that the physician has more time to discuss the findings, their significance, and the child's future care. Written instructions are given to take home.

Summary

Our study showed that on the admission of their child to the hospital parents expressed the greatest anxiety at separation from their child. In an effort to determine how the physician could reduce this anxiety, we found the following to be important:

On admission

1. Adequate preparation of both parent and child for hospitalization. Parents expressed a desire to know

(a) Why the physician was hospitalizing their child and, if possible, what procedures and treatment would be necessary and the risk and discomfort involved;

(b) What to expect in the way of hospital facilities and routine, including knowledge of admission procedures, visiting hours, whether the child would be with other children, whether he would be ambulatory or not, whether he could bring any of his own possessions, the availability of a school teacher, and availability of other facilities to help occupy and distract him—such as toys, TV, radio, etc. Inadequate preparation of the parents reflected on their own poor (or lacking) preparation of the child for hospitalization and further increased separation anxiety on hospital admission.

2. An admission procedure which allowed for a more gradual separation of parent and child.

During hospitalization

To reduce the anxiety of parent and child during hospitalization, the following factors were found to be important:

1. The medical and nursing staff's attitude and concern, as expressed through verbal acknowledgment and management of the child's emotional needs, as well as his physical needs, and the staff's understanding and respect for the parent's concern of the separation from, and care of, their child.

2. The need for continuing preparation and support of parent and child for procedures and treatment during the hospital stay.

At discharge

1. Giving the parents as complete an understanding of our findings and their meaning as possible, in addition to oral and written information necessary for the further care of the child at home.

University of California Medical Center (22).

REFERENCES

1. Prugh, D. G.; Staub, E. M.; Sands, H. H.; Kirschbaum, R. M., and Lenihan, E. A.: A Study of the Emotional Reactions of Children and Families to Hospitalization and Illness, Am. J. Orthopsychiat. 23:70-106 (Jan.) 1953.

2. Powers, G. F.: Humanizing Hospital Experiences: Presidential Address, Am. J. Dis. Child. 76:365-379 (Oct.) 1948.

3. Jackson, E. B.: Treatment of the Young Child in the Hospital, Am. J. Orthopsychiat. 12: 56-67 (Jan.) 1942.

4. Jensen, R. A., and Comly, H. H.: Child-Parent Problems and the Hospital, Nerv. Child 7:200-203 (April) 1948.

5. Gofman, H.; Buckman, W., and Schade, G. H.: The Child's Emotional Response to Hospitalization, A. M. A. J. Dis. Child. 93:157-164 (Feb.) 1957.

6. Health Supervision of Young Children, New York, American Public Health Association, 1955, Chap. 2.

7. Freud, A., and Burlingham, D. T.: Infants Without Families: The Case for and Against Residential Nurseries, Ed. 2, New York, International University Press, 1947.

8. Freud, A.: The Role of Bodily Illness in the Mental Life of Children, Psychoanalyt. Study Child 7:69-81, 1952.

9. Bowlby, J.: Some Pathological Processes Engendered by Early Mother-Child Separation, in Transactions of the Seventh Conference on Problems of Infancy and Childhood, Edited by Milton Senn, New York, Josiah Macy Jr. Foundation, March, 1953, pp. 38-89.

Correspondence

A Letter to a Doctor

EDITORIAL NOTE: *The following letter was given to Dr. Gofman, the author of the previous paper, "Parents' Emotional Response to Child's Hospitalization," by a pediatric colleague. Mrs. Gilbert had written this letter to the consulting ophthalmologist and had sent a copy to her pediatrician. We feel that this letter points up the thesis of the article and, therefore, should accompany it in print. Changes in regulations and routines do not come about easily, but we must remind ourselves and the administrators of our hospitals that children are human beings and need to be treated as such.*

Dear Doctor:

You have just told me that my four-year-old son, Steve, should have a second eye operation in order to further correct the condition of his crossed eyes. With the shocking memory of his recent eye surgery so fresh in both our minds, I consider any hospitalization that is not an emergency an impossibility at this time. It would be preferable for him to have slightly crossed eyes for life than to undergo another such experience. As a parent who takes the sum total of her child's welfare into consideration I can *never* let this second operation occur unless things are handled very differently.

Let me paint the picture of what happened to Steve. I prepared him for his operation and stay in the hospital by telling him what would happen and why. I told him what the doctor was going to do for him and why it was desirable; what a hospital was like, how he would be put to sleep and awaken with one bandaged eye. I told him to call the kind nurses when he needed something. I made it clear to him how long his hospital stay would be and he was reconciled to the fact that there would be times when I could not be with him.

You will remember that I asked that Steve be permitted to enter the hospital on the day of the operation, but you said that you preferred to have patients enter the hospital the day before; it was more "convenient" that way. So for your "convenience," a perfectly well and active four-year-old was placed in a hospital bed in the early afternoon of the day prior to surgery to anticipate his operation for almost 24 hours. He was put in a two-bed room with a small boy who was there for the same purpose as Steve, and frightened by everything. The two boys were companions only in stimulating each other's fears in this strange and unfamiliar room where they could hear the frightened and inexplicable cries of children elsewhere in the building.

On that first afternoon, I left Steve for half an hour to get my husband. When we returned, both boys were in hysterics, alone and working on each other's fright, which had been triggered by a blood test. We spent at least 10 minutes calming them down. It was with great reluctance that my husband and I left the hospital room that night without being allowed to remain until Steve fell asleep for the night.

Until one o'clock the next day, during the preoperative period, Steve had to go without food or water. I was not permitted in the hospital room in spite of entreaties, because I would "be in the way." During that time, Steve's roommate was taken for his operation and returned. I did not see Steve until after he had regained consciousness in the recovery room and had been returned to his room. Neither Steve nor I had been warned that I would not be permitted to be present when he came out from the anesthetic. He awoke completely unprepared for his nightmarish condition. *Both* eyes were bandaged, his arms were bound in splints, and he was tied to the bed. I can find no reason why I should not have been told what to expect, so that I could have prepared Steve for these events which would prove so shocking and terrifying to any four-year-old child.

As soon as the hospital called to tell us that Steve could be released, we rushed to him only to find that he was again in the grip of uncontrollable crying. He was so overheated from this emotional outpouring that I thought, at first, that he was running a high fever. Evidently there were far too few nurses to administer to other than physical needs.

Before the operation, Steve was a well-adjusted, secure, and outgoing youngster and I honestly thought he would be able to go through this experience with a minimum of emotional disturbance. Once home from the hospital, Steve began to have nightmares several times each night, waking and crying out "I want to go home! I want to go home!" This continued until I consulted a child psychiatrist who encouraged him to reenact his experiences in play, allowing him to be the doctor and a doll to be the patient. He played this game avidly for several days, revealing his feelings about his mother leaving him when he needed her, the nasty smell of the ether, the doctor's mask, the bright lights of the operating room, and other

distressing aspects of his experience. When his play operation was over, he turned to me (the nurse), and with great urgency demanded, "Hurry and get his mother. She's in the waiting room. Hurry!"

The nightmares did stop, but he still persists in being a clinging insecure child who puts up a frightened struggle every time I leave him, and is totally unlike the independent child he was before surgery. In the last few months Steve has said to me many times, "You will never take me to a hospital again, will you Mommy?"

I feel sure that this trauma could have been prevented. The long hours before the operation seem unnecessary and the length of the stay afterward probably could have been shortened. Parents should be permitted to stay with their small children in hospitals and should demand to do so. It would seem simple for the doctor or hospital to advise the parent on the necessity of preparing the child to meet every phase of this experience, and to stress the important role the emotionally controlled parent can play, not only in protecting the child from emotional shock but in relieving the hospital staff of some of the individual care after surgery. If I could not be with him, I should want to hire some woman, or find a friend to be with him to ease the way, to explain, to comfort, and to amuse. This is not unreasonable, especially when hospital staffs of paid or volunteer workers are inadequate to administer to more than physical needs.

Just how humane are our doctors and hospitals when it comes to dealing with our pre-school children in these "humane institutions?" A hospital experience, of course, is never thoroughly pleasant for any age, but with small children there is the further consideration of their mental health.

Steve's is no isolated case. I am not alone among mothers who revere the medical profession for its progress toward preserving life and health but who also ask, "What price the 'convenience' of doctors, nurses, and hospitals as against the mental well-being of our small children?"

Sincerely yours,
BETTY GILBERT

Papilledema and Pseudotumor Cerebri Following Poliomyelitis

H. HARVEY GASS, M.D., Detroit

Development of papilledema during the convalescent stage of poliomyelitis is a rare occurrence, and it is not generally recognized as a late complication of the disease. In 1951 Weiman, McDowell, and Plum [1] reported five such cases developing among 106 cases of acute anterior poliomyelitis treated at New York Hospital in the years 1949 and 1950. In their report nine additional cases had been collected from the literature in which this complication appeared to have developed. The present report concerns the occurrence of this complication in two additional patients who suffered from poliomyelitis during the seasonal incidence of 1955 in Detroit and the gratifying prompt response of this complication to subtemporal decompression.

Report of Cases

CASE 1.—A 12-year-old boy was admitted to Sinai Hospital, Detroit, on Oct. 2, 1954, complaining of headache, vomiting, and double vision during the previous week. Two months earlier, on July 27, 1954, after a considerable amount of swimming at a lake, he had complained of being very tired. Two days later he began to have pain in his feet and legs as high as his knees, and he also complained of headache and aching in his back and neck. For the following day he had generalized aching in his entire lower extremities and a temperature of 102. Penicillin and chlortetracycline (Aureomycin) were given, and although his temperature subsided somewhat in the next two days he had difficulty walking and fell. He was admitted to the Elizabeth Kenny Treatment Center on Aug. 4, 1954, where a spinal tap showed a total protein of 56 mg. per 100 cc. and a white blood cell count of 96 per cu. mm. with 95% lymphocytes. His general examination was negative at that time except for a mild injection of his throat and a blood pressure of 150/65. The abdominal reflexes were found to be absent, and a knee jerk was not elicited on the right and was feeble on the left. There was some tightness and tenderness in the posterior neck muscles. Normal power was found throughout the upper extremities, but there was definite weakness throughout the whole right leg. The right anterior tibial, peroneals, posterior tibial, gastrocnemius, soleus, and the toe flexor and extensor muscles all tested trace to poor. The left leg seemed to be good, although there might have been minimal weakness in that extremity. Their diagnosis at that time was anterior poliomyelitis, spinal type. A muscle reeducation program was subsequently started, and the muscle examination on Sept. 9, 1954, revealed all the muscles in the left lower extremity to be essentially normal and in the right all muscle functions rated fair to good.

He continued on his reeducation muscle program and on Sept. 27, 1954, complained of headache and stiff neck. On the following day he developed nausea and vomiting, and the day thereafter he developed double vision. He also complained at the time of admission of a noise in his ear sounding like "jets going by" which was louder on the right.

His past history revealed that he had had measles, chickenpox, and mumps, all before the age of 5, and that he had been vaccinated and had received whooping cough, diphtheria, and tetanus immunizations. A tonsillectomy and adenoidectomy had been performed at the age of 2. A younger brother had had nonparalytic poliomyelitis at the same time that he had had his acute infection.

Examination on Oct. 2, 1954, at Sinai Hospital revealed his blood pressure to be 130/85, pulse rate 84, and respirations 18. His general examination was essentially negative. The neurological examination revealed the presence of bilaterally severe papilledema of about 5 diopters. There was left sixth-nerve weakness with diplopia. (A physician relative of the patient had done a funduscopic examination on this patient during the acute phase of the poliomyelitis, and no papilledema had been present at that time.) There was weakness of dorsiflexion of the right foot and toes, and there

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From the neurosurgical services of Sinai Hospital and Mount Carmel Mercy Hospital.

was a slight steppage gait with his right lower extremity. The right ankle jerk was absent bilaterally. Otherwise there were no other positive neurological findings of significance.

Upon admission his hemoglobin was 13.6 gm. and his red blood cell count was 4,650,000. His white blood cell count was 4550. The urinalysis was normal except for the presence of 2+ albumin. Skull x-rays were normal.

On Oct. 5, 1954, a right cerebral arteriogram was done which was normal. On Oct. 8, 1954, a ventriculogram was performed and the specimen of ventricular fluid showed 3 white cells and 75 red cells per cu. mm., protein 15 mg. per 100 cc., and a sugar of 152 mg. per 100 cc. His ventricular system was normal. At the time of the ventriculogram the dura bulged considerably through the trephine holes and copious amounts of spinal fluid drained through these holes. Immediately after the ventriculogram a right subtemporal decompression was performed. At the time of the subtemporal decompression it was noted that the brain bulged considerably and that it was exceedingly edematous, soft, and wet. His postoperative course was uneventful, and the site of the subtemporal decompression remained full and ballooned out. There was immediate improvement in his headache and other presenting symptoms, and gradual cessation of papilledema. At time of discharge on Oct. 19, 1954, his left sixth-nerve weakness was gone and his papilledema had subsided. The subtemporal decompression, however, was still full.

Examination two months later revealed normal disks, normal extraocular muscle movement, and an asymptomatic state. The decompression site in his right temple was bulging and full but was soft. By report it was decreasing in size. When last seen eight months following surgery he was again asymptomatic, and the bulging at the decompression site had now gone and new bone plaques could be palpated at the site. Skull x-rays at this time confirmed the fact that new bone formation was developing across the old craniectomy gap.

CASE 2.—This 7-year-old boy was admitted to Mt. Carmel Mercy Hospital on Nov. 15, 1954, complaining of headaches and double vision. About two months earlier, on Sept. 8, 1954, he began to complain of gas pains and the following day of pain in his neck. On Sept. 10, 1954, he was very tired and had backache, headache, and pains in the back of his neck. Fever was also noted at this date. He was admitted to Herman Kiefer Hospital on Sept. 10, 1954, with a diagnosis of suspected poliomyelitis. Examination at that time revealed him to have moderate rigidity of his neck and back, slight enlargement of his cervical lymph nodes, and a systolic murmur at the base of the heart. The diagnosis of poliomyelitis, nonparalytic type, was confirmed at that hospital on Sept. 14, 1954. A spinal-fluid examination at that time revealed a cell count of 115, all polymorphonuclear leukocytes. Sugar was normal by the qualitative method at that time. His temperature returned to normal from an admission temperature of 101 by the fourth day. Treatment consisted of physical therapy procedures, but no hot packs were considered necessary. He was discharged from Herman Kiefer Hospital on Sept. 18, 1954, with a final diagnosis of poliomyelitis, nonparalytic type.

He remained well until one week prior to admission to Mt. Carmel Mercy Hospital when he began to vomit and have intermittent headache. Three days prior to admission the headache became severe and localized over his right eye. A day later the severe headache persisted but was maximum in the left temporofrontal region and he developed double vision. He remained lethargic and drowzy until the time of admission.

His past history revealed that he had previously had measles and chickenpox without any complication. Tonsillectomy and adenoidectomy had been performed at the age of 4½. The family history was not contributory. On the day of admission he was seen by an ophthalmologist, who found his visual fields to be normal. Marked bilateral papilledema, however, was present, and there was right sixth-nerve weakness.

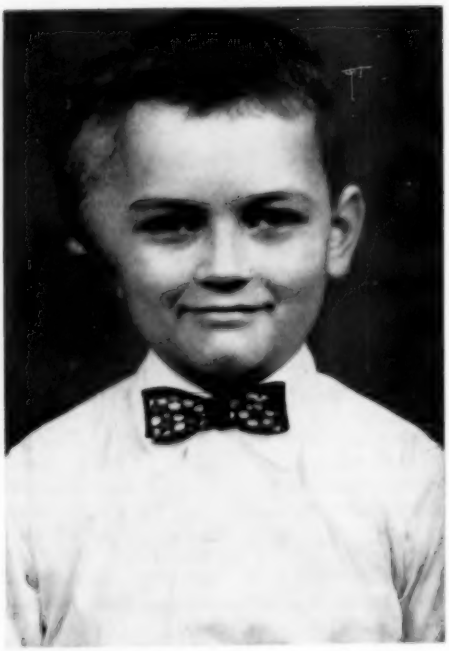
Examination on Nov. 15, 1954, on admission to Mt. Carmel Mercy Hospital revealed his blood pressure to be 127/75, pulse rate 80, respirations 60. His physical and neurological examinations were negative except for the papilledema and weakness of his right sixth nerve.

Laboratory examinations revealed the hemoglobin to be 14.4 gm., the red blood cell count to be 5,140,000, and his white blood cell count to be 6400. Urine examination was negative. X-rays of his skull and optic foramina were negative.

On Nov. 21, 1954, his right sixth-nerve weakness was increased and the papilledema had also advanced with more exudate and hemorrhages. On Nov. 21, 1954, a stool specimen was sent to the Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, for virus study for possible identification of poliomyelitis virus.* (Subsequent reports failed to identify the presence of poliomyelitis virus in this late specimen.)

A ventriculogram was done on Nov. 22, 1954, and fluid from the ventricular system revealed six red cells and four white cells per cu. mm., negative Pandy test, and the protein was 6 mg. per 100 cc. At that time fluid obtained from the subdural space revealed a red blood cell count of 100 per cu. mm., white blood cell count of 15 per cu. mm., a trace in the Pandy test, and protein of 41 mg. per 100 cc. The ventricular system was normal by x-ray at this time.

* Courtesy of Dr. Gordon Brown.



Case 2. Subtemporal decompression still effective two and one half months after surgery.

On the same day a right subtemporal decompression was done. There was considerable bulging of the dura noted at this time. Both at this procedure and at the ventriculogram considerable amounts of spinal fluid drained throughout the procedure. The brain appeared to be wet, edematous, and swollen.

His postoperative course was uneventful, and there was immediate improvement in double vision and headache and gradual but steady improvement in his papilledema. He was discharged on Dec. 3, 1954, with the site of decompression still markedly swollen and no evidence of extraocular motor palsy being present. The papilledema was nearly entirely gone.

He was seen on several occasions during the next year, and during each time he was asymptomatic, his funduscopic examination was normal, and there was no ocular-motor-muscle weakness. For about five months his decompression site remained full but soft (Figure). At that time the fullness began to be only at the lower end of the decompression and new bone began to be palpated at this site starting to bridge the craniectomy gap. On Jan. 9, 1956, the entire craniectomy gap was nearly filled with new palpable bone formation.

Comment

It is of interest that the two patients here presented ran almost identical courses with respect to the time of onset of symptoms after their acute poliomyelitis infection, approximately two months after the acute disease, the type and development of symptoms, the prompt response to subtemporal decompression, and the regrowth of new bone at the decompression site making a subsequent cranioplasty unnecessary in either patient.

In Case 2 the diagnosis of poliomyelitis could not be proved by isolation of the virus from the stool at the time papilledema had developed. It is the rule, however, that demonstration of poliomyelitis virus in nonparalytic cases as long as two months after the acute infection is usually not possible.[2] The clinical circumstances, however, leave the weight of evidence in favor of poliomyelitis. During the height of the poliomyelitis season he was admitted to Herman Kiefer Hospital after a three-day illness with headache, pains in the back and neck, and fever. The diagnosis of poliomyelitis was suggested there after a spinal tap which showed a cell count of 115 white blood cells. On clinical grounds alone the diagnosis of poliomyelitis in Case 1 seems reasonable.

The syndrome of headache and bilateral papilledema in nonhypertensive, nontoxic patients without intracranial suppuration or hemorrhage who upon neuroradiological studies fail to demonstrate a mass lesion or hydrocephalus has been referred to as pseudotumor cerebri, serous meningitis, hypertensive meningeal hydrops, benign intracranial hypertension, or otitic hydrocephalus. Such patients, therefore, represent a group presenting with bilateral papilledema, and they, therefore, are considered to be brain-tumor suspects, but upon investigation they prove not to have a space-occupying lesion. The etiology of these cases is often un-

clear. Some have been shown to be due to thrombosis of the sagittal sinus.[3] Symonds[4] believes that in those who have a preexisting otitis media the condition develops because of thrombosis of the homolateral sinus and that these patients also have a congenitally absent or deficient contralateral lateral sinus. This situation thus is equivalent to a sagittal sinus thrombosis. The sixth-nerve palsy characteristic of otitic hydrocephalus, often attributed to petrositis with involvement of the adjacent sixth nerve, he believes is due to the impingement of the sixth nerve as it passes through a forked inferior petrosal sinus, both branches of which are effected by thrombophlebitis. Cerebral edema, both posttraumatic and menstrual, may also produce this syndrome. Increased intracranial venous pressure secondary to congestive heart failure as a cause of papilledema is not unknown and may fit this category. Recently Jefferson[5] has brought attention to the possible presence of this syndrome in Addison's disease. I have also had experience with such a case in a 16-year-old girl with unexplained papilledema, Addisonian pigmentation, and adrenal failure. Yaskin, Groff, and Shenkin[6] have noted pseudotumor cerebri in diffuse infections of the central nervous system. Bradshaw[7] has added inflammation and infections of the second branchial cleft, extracranial venous thrombosis, obesity, and cortical thrombophlebitis as additional specific etiological agents operating in the production of this syndrome. Despite these specific causes, a large number of the complications in such patients remain unexplained. Zuidema and Cohen[8] in a follow-up study of 80 cases in the Johns Hopkins Hospital records were unable to satisfactorily demonstrate a specific cause in at least 39 such cases.

Postpoliomyelitis papilledema fits the criteria of pseudotumor cerebri as outlined above. Although these cases by definition fall into this category, as in other instances, by the very fact that a specific etiology is responsible, they may be separated from it. As future clinical knowledge accumulates, in all such pseudotumor cerebri patients an adequate explanation for development of this syndrome may be found. The retention of the entity in clinical classification would then seem to be a redundancy were it not for the fact that patients suffering it are suspected initially of having an intracranial mass and also that generally they share a favorable prognosis for life. Although any underlying disease itself which may coexist, such as congestive heart failure, Addison's disease, poliomyelitis, etc., may have a fatal termination, the cerebral component producing the increased intracranial pressure does not imply a fatal pathological mechanism per se, and in time the papilledema may be expected to spontaneously recede. Many cases have been noted to pursue a benign course with complete reversal of all signs and symptoms to normalcy, even without treatment. Some have been managed successfully by multiple spinal taps and drainage or dehydration. The duration of the disease may be variable, lasting weeks to months. Weiman et al.[1] observed their five cases of postpoliomyelitis papilledema clear up in from 13 days to 140 days without definitive treatment. This time interval for reversal is comparable to common experience with other forms of pseudotumor cerebri. A note of caution should be inserted here to emphasize that some patients who after neuroradiological investigation fall into this category may on subsequent reevaluation weeks or months later prove to have brain tumors which were previously unidentifiable.

Aside from the need to control symptoms of headache and blurred vision, the chief indication for more vigorous surgical therapy in the form of subtemporal decompression is the preservation of

vision. When the papilledema is severe enough to produce subjective visual blurring and loss of visual acuity or when diplopia of the patient is chronic, the threat of significant visual loss from secondary optic atrophy or from amblyopia secondary to ocular palsy may be great. Yaskin et al.[6] noted that in 5 of 10 of their surviving patients secondary optic atrophy developed. They stated, "We feel reasonably certain that two of our patients owe whatever vision remains to a subtemporal decompression." Following such a procedure, whatever headache has been present is also relieved. It is noteworthy, however, that the headache in pseudotumor cerebri is less severe than that due to increased intracranial pressure of a comparable degree from brain tumor.

The circumstances of severe papilledema with blurred vision and ocular palsy with diplopia, both representing a serious threat to vision in each of these cases, were the factors which made me decide upon subtemporal decompression as the preferential treatment. Headaches were not severe in either patient. Prompt response postoperatively of both the papilledema and ocular palsies was gratifying.

The explanation of why this complication should develop and why it should be delayed until the convalescent stage is not clear. A suggestion is offered in the experience of Ayer and Trevett[9] and of Weiman, McDowell, and Plum.[1] In Ayer and Trevett's case the development of papilledema one month after the appearance of paralytic manifestations was associated with pleocytosis and increased cerebrospinal fluid protein. The latter and the cerebrospinal fluid pressure remained elevated for at least five months. In three of the five cases of Weiman et al. spinal-fluid protein was obtained at the time of papilledema and was found to be 147, 162, and 306 mg. per 100 cc. Gardner, Spitler, and Whitten[10] have drawn attention to the relationship of increased intracranial pressure to increased protein content in the spinal fluid. They believe that the increase in pressure is due to the mechanical clogging by the protein molecules of the pores of the semipermeable membrane that constitutes the blood-brain barrier. This explanation of the development of papilledema in the cases of Ayer and Trevett and of Weiman, McDowell, and Plum, if valid, however, cannot be applied to the cases in this report, since in Case 1 the ventricular fluid showed a protein of only 15 mg. per 100 cc. and in Case 2 the protein of the ventricular fluid was 6 mg. per 100 cc. There was no reason to suspect a pathological discrepancy between the spinal fluid and the ventricular fluid proteins in these cases, since obstructive hydrocephalus was not present. In Case 2 a thin layer of subdural fluid was found, and the protein in this fluid was 41 mg. per 100 cc. The quantity of this fluid present over the convexity of the brain was inadequate in this location to suggest an explanation for the marked papilledema in this patient on the grounds of a pathological subdural effusion creating underlying brain compression. It was a free-flowing unencapsulated layer of fluid not producing any visible localized compression of the brain.

In both of these cases as well as in other instances of pseudotumor cerebri we have been impressed with the quantity of cerebrospinal fluid which flows out of the subdural space before the arachnoid is disturbed. Sometimes the brain may bulge into the trephine hole sealing off the escape of subdural fluid, but this flow may be reestablished by gently depressing the brain from the edges of the trephine hole. When enough fluid has escaped, the brain ceases to bulge. The fluid does not appear to be enclosed in a

membrane of its own in such circumstances, as one finds with a chronic subdural hematoma. Moreover, one cannot visualize a significant depression of the brain away from the calvarium as is seen in other encapsulated subdural collections. The fact that the brain is not locally depressed, however, does not mean that a relatively large amount of freely flowing fluid may not circulate in the entire cerebral subdural space, thus creating generalized uniform cerebral compression.

Except in those instances in which trauma has occurred to account for an arachnoid tear which permits ingress of cerebrospinal fluid into the subdural space without an avenue of escape, there appears to be no satisfactory explanation of how fluid may thus accumulate in the subdural space, if, indeed, such a process operates in the production of this entity. McConnell [11] has offered such a trapping of cerebrospinal fluid in the subdural space as a cause of "post-traumatic syndrome," but in his cases the protein content of this trapped fluid was greatly elevated to levels of 200 mg. per 100 cc. and higher, and papilledema was generally not present. In Case 2 it was 41 mg. per 100 cc., while the ventricular fluid protein was only 6 mg. per 100 cc. If the accumulation of subdural fluid is a significant etiological factor in the production of pseudotumor cerebri as it appears to be in some instances, an explanation is wanting of how or why this develops in nontraumatic cases. Increased cerebrospinal fluid protein as in Ayer and Trevett's case and in three of the five cases of Weiman et al. is the only other explanation apparent for the development of postpoliomyelitis papilledema. Indeed, Ayer and Trevett [9] mention that in 20 cases of poliomyelitis during the 7th to 13th week after the infection protein values of 200 to 300 mg. per 100 cc. were found. Some other explanation must be sought, however, in the case of Voisin and Bonduelle,[12] referred to in the report of Weiman et al., in whom the protein was only 65 mg. per 100 cc. and in the present two cases in whom no elevation of ventricular fluid protein was present. The role of excessive quantities of fluid in the subdural space is unclear but may be an etiological factor in the development of this syndrome in certain instances of postpoliomyelitis papilledema as well as in other instances of pseudotumor cerebri.

Summary

Two cases are presented of the development of severe papilledema following poliomyelitis.

The gratifying response in both patients to subtemporal decompression is stressed.

612 Kales Building (26).

REFERENCES

1. Weiman, C. G.; McDowell, F. H., and Plum, F.: Papilledema in Poliomyelitis, A. M. A. Arch. Neurol. & Psychiat. 66:722-727, 1951.

2. Brown, G. D., Department of Epidemiology, University of Michigan, School of Public Health, Ann Arbor, Mich., personal communication to the author.

3. Ray, B. S.; Dunbar, H. S., and Dotter, C. T.: Symposium: Intracranial Vascular Abnormalities: Dural Sinus Venography as an Aid to Diagnosis in Intracranial Disease, J. Neurosurg. 8:23-37, 1951.

4. Symonds, C.: Otitic Hydrocephalus, Presented at the 8th Annual Meeting, American Academy of Neurology, St. Louis, April 28, 1956.

5. Jefferson, A.: A Clinical Correlation Between Encephalopathy and Papilloedema in Addison's Disease, J. Neurol. Neurosurg. & Psychiat. 19: 21-27, 1956.

6. Yaskin, J. C.; Groff, R. A., and Shenkin, H. A.: Severe Papilledema in Diffuse Infections of the Nervous System, Tr. Am. Neurol. A. 72: 27-41, 1956.

7. Bradshaw, P.: Benign Intracranial Hypertension, J. Neurol. Neurosurg. & Psychiat. 19: 28-41, 1956.

8. Zuidema, G. D., and Cohen, S. J.: Pseudotumor Cerebri, J. Neurosurg. 11:433-441, 1954.

9. Ayer, J. B., and Trevett, L. D.: Acute Poliomyelitis with Choked Disks: Notes on Prolonged Observation of the Spinal Fluid and the Use of the Respirator, Arch. Neurol. & Psychiat. 31: 396-402, 1934.

10. Gardner, W. J.; Spitler, D. K., and Whitten, C.: Increased Intracranial Pressure Caused by Increased Protein Content in the Cerebrospinal Fluid, New England J. Med. 250:932-936, 1954.

11. McConnell, A. A.: On Certain Sequelae of Closed Head Injuries: The Pathological Basis of the "Post-Traumatic Syndrome," Brain 76:473-484, 1953.

12. Voisin, J., and Bonduelle, M.: Syndrome méningé à rechute avec stase papillaire importante au cours d'une poliomyélite antérieure aiguë, Rev. neurol. 79:39-40, 1947.

Childhood Accidents and Their Prevention

HAROLD JACOBZINER, M.D., New York

Magnitude and Scope of the Problem

Three persons will die and about four hundred fifty persons will suffer injury from accidental causes in the United States during the course of this presentation.

Ninety-two thousand (92,000) persons died from accidents last year and more than 9,200,000 injuries were reported in the United States in the same period. One-third of the injuries resulted in permanent damage. The cost in life and property exceeded ten billion dollars.

Fourteen thousand fatalities occurred in children under 15 years of age. Twenty-seven thousand five hundred (27,500) deaths and more than four million injuries resulted from home accidents. Of those killed in home accidents, 5700, or more than 20%, were children under 5 years old.[1]

Accidents are the leading cause of death from 1 to 34 years and the fourth leading cause in persons of all ages. It ranks seventh in the under-one-year age group. More deaths and injuries result from acci-

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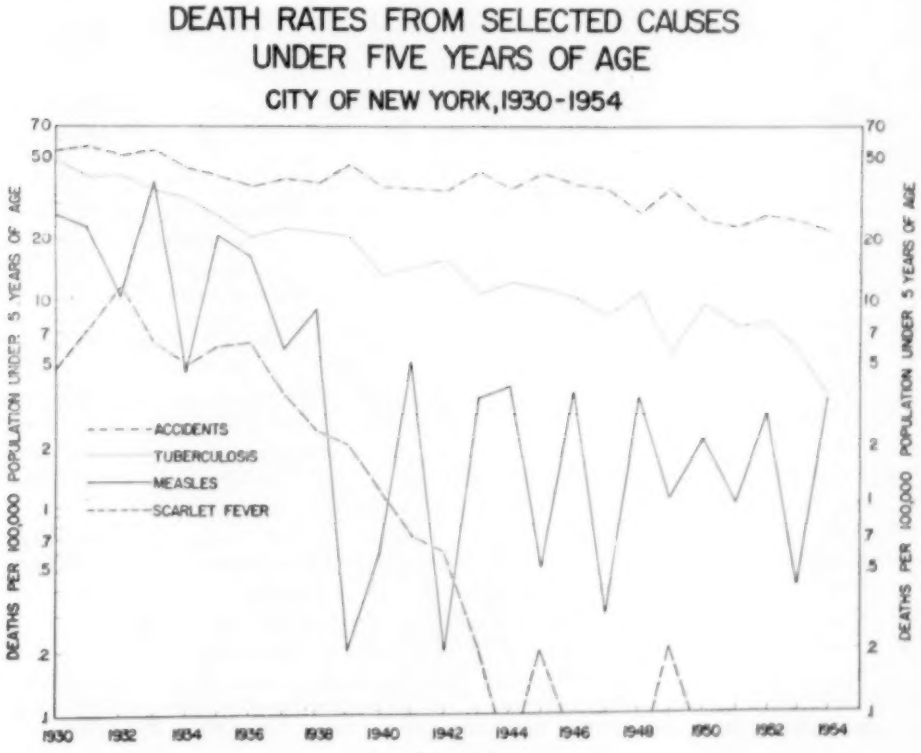

Figure 1

dents in children from 1 through 14 years of age than from any other illness or disease condition.

In New York City, in 1954, accidents were responsible for more deaths in the under-5-year age group than twice the number of the 10 leading communicable diseases combined. From 5 through 14 years, accidents again killed more children than any other disease condition commonly found in this age group.

Except for malignant neoplasms, accidents are responsible for exactly the same number of deaths as the other six chief causes combined (i. e., 135 deaths).

Accidents also were at the head of the list at ages 15-24 and caused appreciably more deaths than any other leading cause.

Owing to marked advances in medicine and public health, childhood deaths have declined precipitously in the past 25 years. Death rates from accidents, however, did not share in this decline to the same degree (Figs. 1, 2 and 3).

The above data are not intended to minimize the importance of the other disease conditions but rather to put "accidents" in their proper perspective as a major public health problem and as the leading cause of mortality and morbidity in young children.

It is paradoxical that in spite of the enormity of the problem but little focus and attention have been harnessed in its solution. Until recently all our knowledge about accidents was derived from studies of fatal accidents. Little if anything was known about nonfatal accidents.

More than a decade ago, however, Gordon [2] and others [3,4] postulated that accidents may be amenable to control with the application of epidemiologic principles and that epidemiologic methods are just as worth-

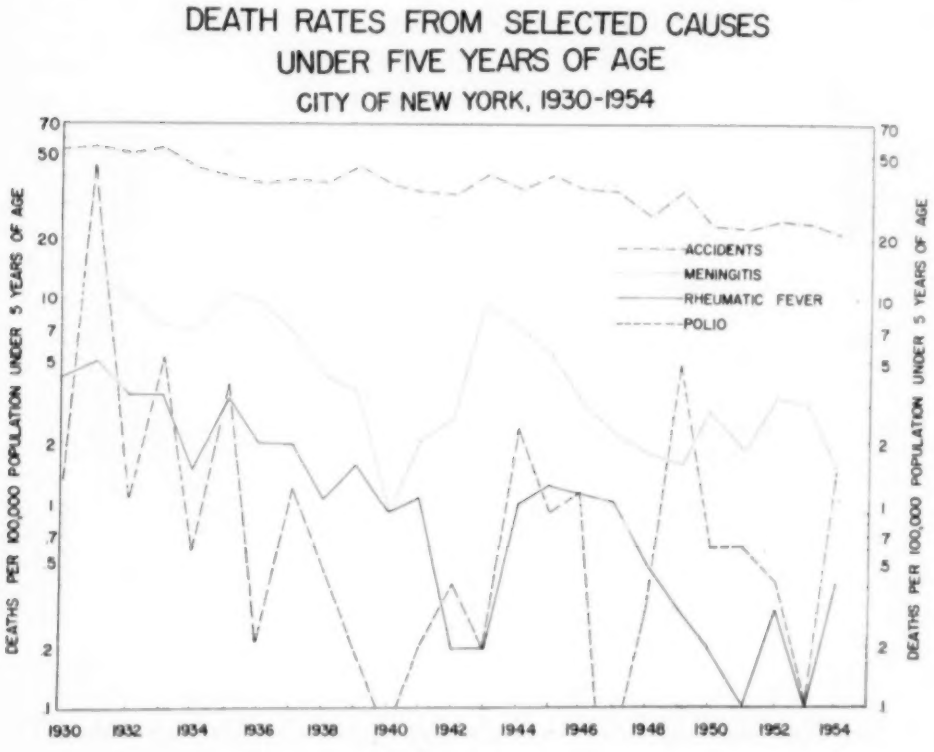

Figure 2

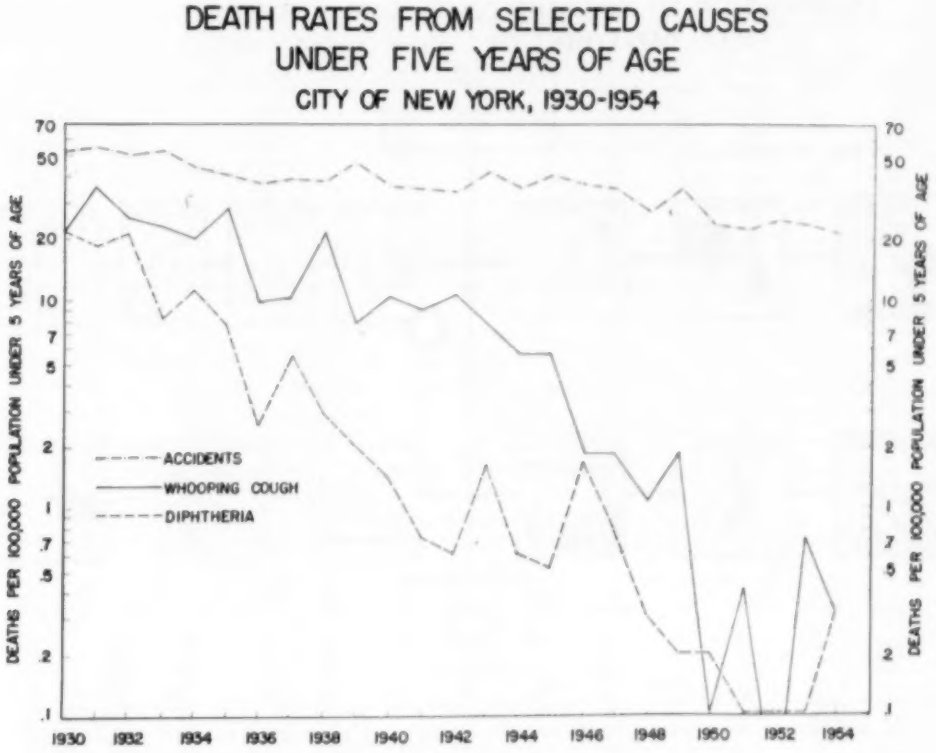

Figure 3

while in accident control as in the control of communicable diseases.

A Plan for Action

In 1951 the New York City Department of Health became vitally concerned with the solution of the accident problem and inaugurated a threefold program of (1) staff education, (2) parent education, (3) epidemiological investigation.

The epidemiological investigations were designed to obtain precise data about the natural history of accidents in children both fatal and nonfatal.[5]

Accident prevention has become an integral part of the direct service program in the 80 child health stations throughout the city. The physician inquires about the occurrence of an accident to a child or sibling in the same manner as about past illnesses, and if a positive history is obtained findings are reported on a specially designed form. In addition to identifying data it also includes information on sex, race, type of accident, place of occurrence, season, time of day, activity at time of accident, type of supervision, and many other still unidentified and undetermined associated factors.

Home epidemiologic investigations are also made on fatal cases and all poisonings.[6] Because of the importance of accidents as a cause of death and disability and because accident control has many facets and requires a team approach in its solution, the Commissioner of Health established, in 1954, a Task Force on Accident Prevention.[7]

The mission of the Task Force is to study and appraise the current activities of the Department and to plan and direct appropriate expansion of the programs. The com-

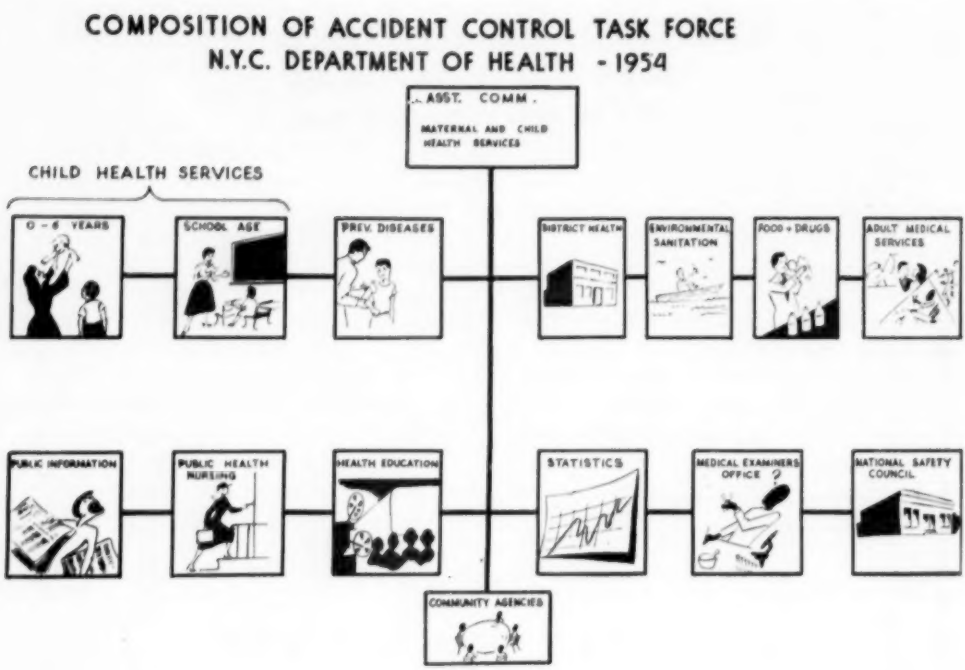

Figure 4

position of the Task Force represents all skills and disciplines working harmoniously together toward a common goal (Fig. 4).

In order to combat and control chemical poisonings, a Poison Control Center was established in 1955.[8-10]

It provides to practicing physicians and hospitals reliable information and services for the management of chemical poisonings.

The Poison Control Center serves as a focal information and diagnostic facility where data are compiled, inquiries are received, information is disseminated, and needed diagnostic laboratory facilities are made available as indicated.

All epidemiological data are carefully collected, tabulated, and scrutinized. It is believed that based upon this knowledge, sound preventive measures may be instituted which will result in a control and ultimate elimination of many accidental poisonings.

Home Visiting

A district public health nurse in the area involved makes a home visit to interview families about all fatal accidents and all accidental poisonings in children under 16 to obtain the needed epidemiologic data. In addition to the queries about the accident, the public health nurse is also requested to comment on whether any other health problems exist in the home, action taken, and type of follow-up planned. The public health nurse also comments on the attitude of the family toward the interview, acceptance of nurse's visit, whether the accident was preventable and whether such visits are helpful in preventing further accidents.

The nurse is also requested to state whether this kind of an activity is of any educational or practical value to her.

Results of Investigations

Age, sex, and race variations in 3000 nonfatal accidents reported in children under supervision in child health stations are presented in Table 1.

Sex.—There were 56.8% boys and 43.2% girls, a statistically significant preponderance of boys.

TABLE 1.—*Age at Time of Accident with Regard to Sex and Color*

Age in Months*	Total				Boys				Girls			
	Total	White	Puerto Rican†	Non-white‡	Total	White	Puerto Rican†	Non-white‡	Total	White	Puerto Rican†	Non-white‡
Under 6	189	60	42	87	103	36	22	45	86	24	20	42
6 -11	408	203	65	140	217	105	33	79	191	98	32	61
12-17	522	276	60	177	308	169	46	93	214	107	25	84
18-23	416	228	53	135	232	128	32	72	184	100	21	63
24-35	555	344	48	163	314	190	34	81	241	145	14	82
36-47	429	276	50	103	264	183	25	56	165	93	25	47
48-59	309	196	30	83	176	114	14	48	133	82	16	35
60 and over	149	95	21	33	77	52	9	16	72	43	12	17
Unknown	23	14	1	8	13	10		3	10	4	1	5
Total	3,000	1,692	379	929	1,704	996	215	493	1,296	696	164	436

* Six-month intervals for the first two years of life; year intervals for two through four years.
† Not a color, but kept as a group for this study.
‡ Includes unknown.

Race.—There were 32.3% of the accidents reported in nonwhite children. This is more than twice the nonwhite distribution in the general population in New York City; hence the race preponderance is statistically valid. Since the race composition of the child health station population is not accurately known, no definite conclusions will be drawn as to variations by race.

Age.—The 12-17 month age group is the most susceptible (the creeper and the toddler are highly vulnerable), accounting for 17.4% of all accidents, a higher incidence than at any other six months age interval. It is true for the white and nonwhite and for both sexes alike.

TABLE 2.—*Age at Time of Serious* Accident with Regard to Sex and Color*

Age in Months†	Total				Boys				Girls			
	Total	White	Puerto Rican‡	Non-white§	Total	White	Puerto Rican‡	Non-white§	Total	White	Puerto Rican‡	Non-white§
Under 6	99	35	21	43	55	20	13	22	44	15	8	21
6 -11	187	102	28	57	93	52	13	28	94	50	15	29
12-17	281	139	46	96	169	85	32	52	112	54	14	44
18-23	215	120	28	67	124	69	18	37	91	51	10	30
24-35	328	206	26	96	185	121	18	46	143	85	8	50
36-47	255	169	36	50	167	116	21	30	88	53	15	20
48-59	195	134	17	44	117	80	10	27	78	54	7	17
60 and over	95	69	7	19	86	41	5	10	39	28	2	9
Unknown	12	9	1	2	7	7	...	...	5	2	1	2
Total	1,667	983	210	474	973	591	130	252	694	392	80	222

* Defined as receiving some medical care (private physician, outpatient department, inpatient department).
† Six-month intervals for first two years of life; year intervals for two through four years.
‡ Not a color, but kept as a group for this study.
§ Includes unknown.

Serious Accidents (Table 2).—More than 55% were serious accidents. The distribution by age, sex, and color is essentially the same as for all accidents.

Incidence by Age and Sex (Table 3).—Boys have a higher incidence for all acci-

TABLE 3.—*Age at Time of Accident with Percentages for Sex Incidence*

Age in Months*	A. All Accidents						B. Serious Accidents†					
	Total		Boys		Girls		Total		Boys		Girls	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Under 6	189	100.0	103	54.3	86	45.7	99	100.0	55	55.6	44	44.4
6 -11	408	100.0	217	53.2	191	46.8	187	100.0	93	49.7	94	50.3
12-17	522	100.0	308	59.0	214	41.0	281	100.0	169	60.1	112	39.9
18-23	416	100.0	232	55.8	184	44.2	215	100.0	124	57.7	91	42.3
24-35	555	100.0	314	56.6	241	43.4	328	100.0	185	56.4	143	43.6
36-47	429	100.0	264	61.5	165	38.5	255	100.0	167	65.5	88	34.5
48-59	309	100.0	176	57.0	133	43.0	195	100.0	117	60.0	78	40.0
60 and over	149	100.0	77	52.0	72	48.0	95	100.0	56	58.9	39	41.1
Unknown	23	100.0	13	56.5	10	43.5	12	100.0	7	58.3	5	41.7
Total	3,000	100.0	1,704	56.8	1,296	43.2	1,667	100.0	973	58.4	694	41.6

† Defined as receiving some medical care (private physician, outpatient department, inpatient department).
* Six-month intervals for first two years of life; year intervals for two through four years.

TABLE 4.—*Age at Time of Accident with Percentages for Age Incidence*

Age in Months*	A. All Accidents						B. Serious Accidents†					
	Total		Boys		Girls		Total		Boys		Girls	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Under 6	189	6.2	103	6.0	86	6.6	99	5.9	55	5.6	44	6.4
6–11	408	13.6	217	12.7	191	14.7	187	11.2	93	9.6	94	13.6
12–17	522	17.4	308	18.1	214	16.5	281	16.9	169	17.4	112	16.1
18–23	416	13.9	232	13.6	184	14.2	215	12.9	124	12.7	91	13.1
24–35	555	18.5	314	18.4	241	18.6	328	19.7	185	19.0	143	20.6
36–47	429	14.3	264	15.5	165	12.7	255	15.3	167	17.2	88	12.7
48–59	309	10.3	176	10.3	133	10.3	195	11.7	117	12.0	78	11.2
60 and over	149	5.0	77	4.6	72	5.6	95	5.7	56	5.8	39	5.6
Unknown	13	0.8	13	0.8	10	0.8	12	0.7	7	0.7	5	0.7
Total	3,000	100.0	1,704	100.0	1,296	100.0	1,667	100.0	973	100.0	694	100.0

* Six-month intervals for first two years of life; year intervals for two through four years.
† Defined as receiving some medical care (private physician, outpatient department, inpatient department).

dents at all ages. The highest male preponderance is observed at age 36-47 months and the lowest at 5 years and over.

For serious accidents the sex distribution is about equal at ages 6-11 months, (the female incidence, as a matter of fact, slightly exceeding the male); however, there is a marked rise in the male incidence at the next age category, i. e., 12-17 months. The highest male incidence for serious accidents is also at ages 36-47 months. The girl after one year is probably less venturesome and more cautious than the boy and hence less vulnerable. The relative incidence of all accidents and serious accidents with percentages by age is shown in Table 4.

Seasonal Variations.—In a prior study [5] on nonfatal accidents in a comparable population group, it was observed that there is a higher incidence of serious accidents dur-

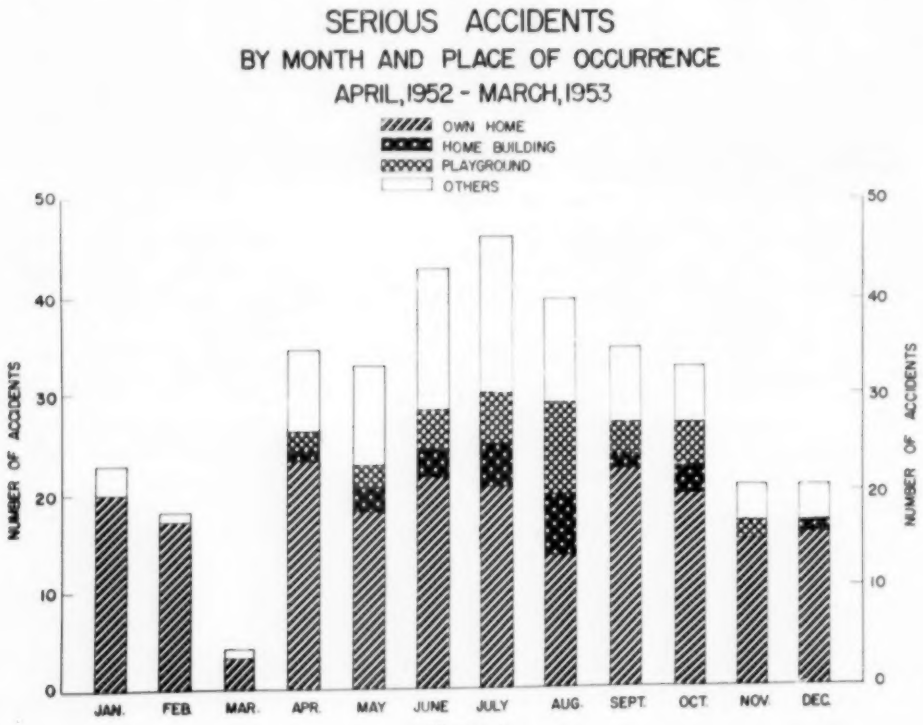

Figure 5

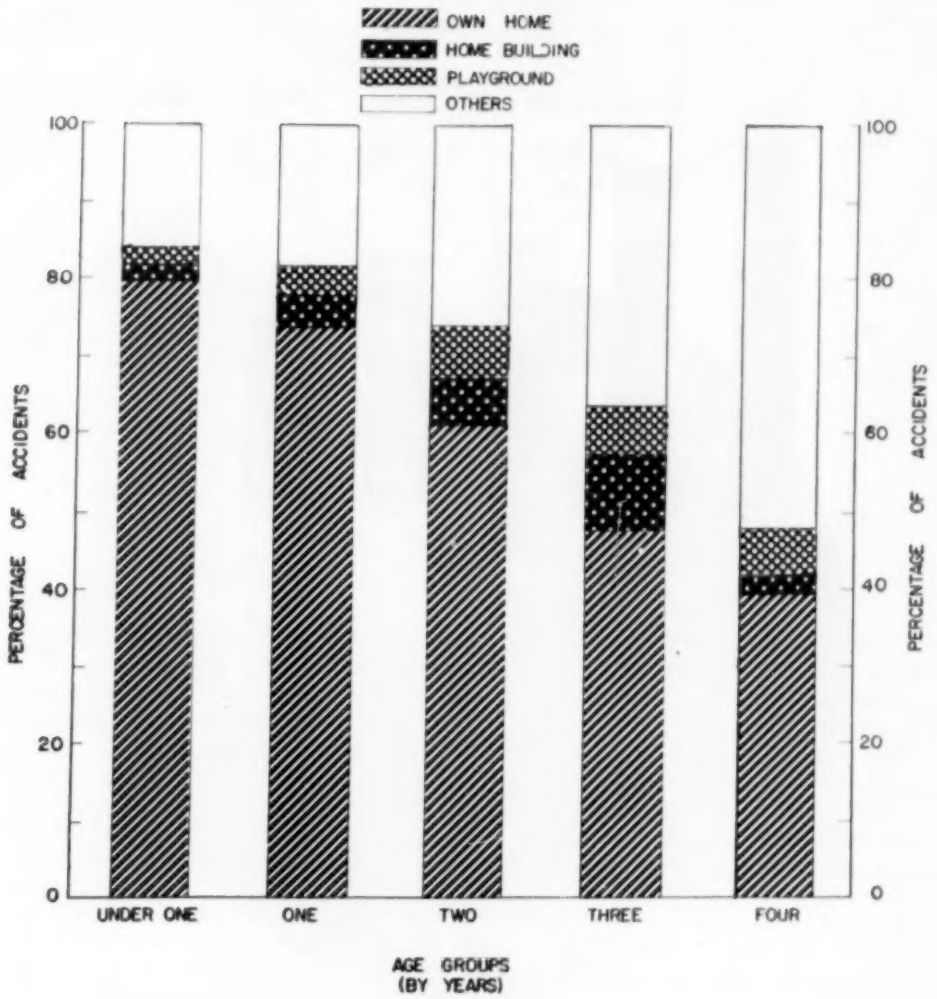

Figure 6

ing the summer and spring and a much lower incidence in the fall and winter. The seasonal variation is particularly marked in lead poisonings (Fig. 5).

Place of Occurrence (Fig. 6).—It was also found in that study that only 18.2% of the total number of 1000 accidents occurred outdoors, such as playground, yard, or street, and that nearly all of the outdoor variety was of a "serious" nature. Several reasons were postulated for this finding, such as greater hazards of play, lack of adult supervision, and the possibility that minor outdoor accidents were not reported to the parents.

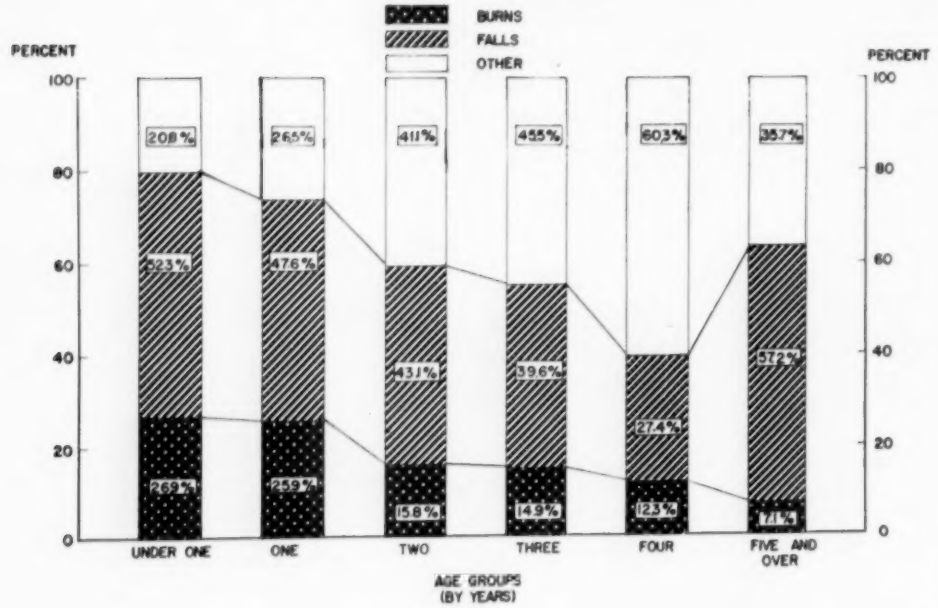

Figure 7

Type of Accident by Age (Fig. 7).—Falls were the most frequent injuries encountered, 45% of the total number. Burns were next with an incidence of 21.5%. Falls and burns together accounted for nearly 67% of all reported mishaps.

Falls alone were responsible for more than 50% of all mishaps in the under-one-year age group and diminishing steadily with advancing age to a low of 27% at age 4. A sharp upturn, however, is noted at age 5 and over. This increase is associated with the particular stage of growth and development when children of this age group are exposed to greater risks. Children of 5 years and over are generally more daring, adventuresome, and show greater exploration and mobility in pattern of play activities.

Burns showed a like pattern. Highest incidence in the under-one-year group, about 27% of all reported injuries in this age group and steadily declining with advancing age to 7% in the 5-year-and-above age category. Burns did not show the rise noted in falls, possibly because of previous experience with "fire" and "hot" substances—the child has learned greater caution.

Pathogenesis.—Falls resulted mainly from climbing, running, walking, slipping while playing. Burns were due in the main to contact with fire and with hot substances.

Poisonings occurred chiefly because of accidental ingestion of medications and household preparations in over 90% of the cases through self-administration. In only a negligible number was it due to an error on the part of the physician.

Other pertinent observations in this study and in previous surveys [11] were as follows: (1) Accidents are preventable in more than 90% of cases. (2) There was a lack of adult supervision at the time and place of accidental occurrence.

Repeatism (Accident Proneness).[10-11]—Another interesting finding was a lack of

accident proneness in this age group. Only 19 children out of a total of 981 had more than one occurrence, and none experienced more than two accidents during their lifetime. This observation is in variance with findings of other observers. It is possible that the pattern of accident proneness does not become manifest till after age 6 years. This subject deserves further research and scrutiny.

Accidents Due to Chemical Poisonings.—Though poisonings were reportable for

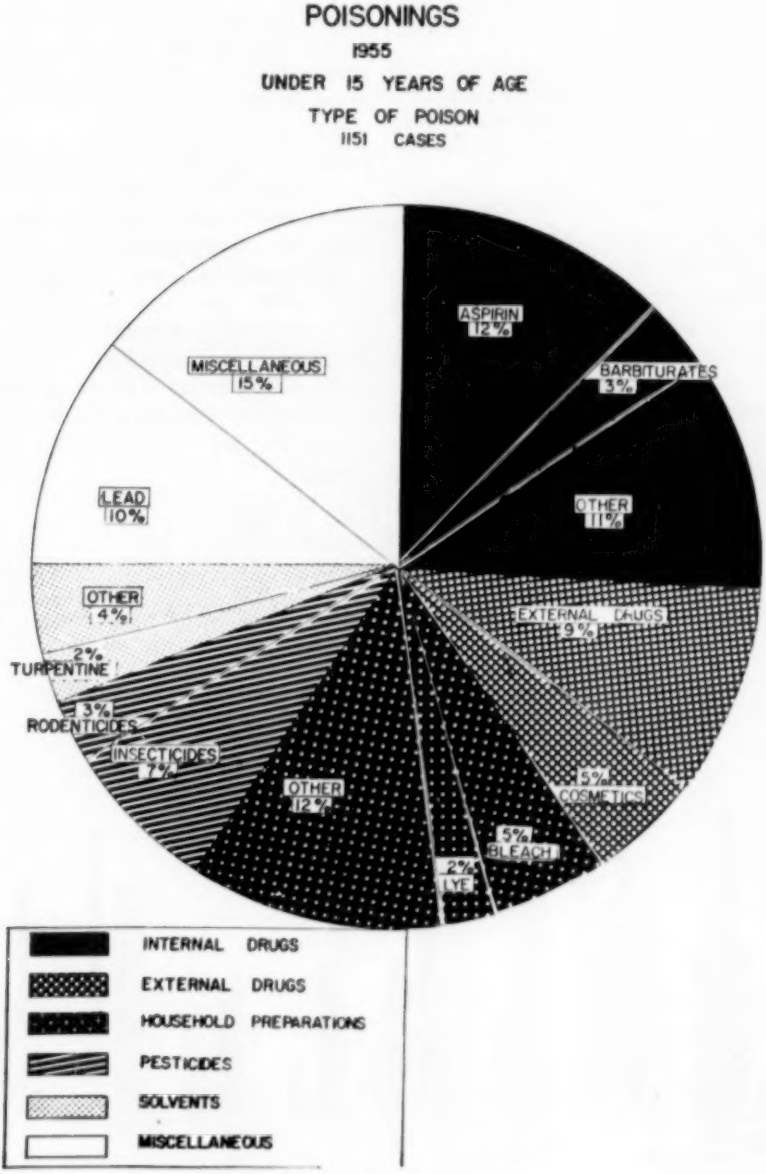

Figure 8

many years in New York City, they were in the main unreported, owing to the lack of awareness on the part of the practicing physician. Some incomplete and indirect information was available from a study of fatal poisonings. About 20 fatal poisonings were reported in children under 5 years annually. Since it is estimated that for every fatal incident there are about 125-150 nonfatal occurrences, it was believed that about 2000 chemical poisonings (gas excepted) occur annually in this age group, though only a handful were actually reported.

Since the establishment of the Poison Control Center, however, reporting has improved markedly, and for the first 9 months 1151 incidents were reported in children under 15.

Figure 8 (Poison Pie) represents a breakdown of poisonings by generic categories. These include several hundred distinct clinical entities, and many are contained in various brands.

No drug or household preparation is exempt.

It may be well to cite actual incidents reported in a recent 24-hour period.

The diversity and multiplicity of substances involved is best illustrated by mentioning the injurious agents incriminated in actual occurrences in a recent 24-hour period (June 20, date of writing of this report).

Seventeen specific incidents were reported; the ages of the children ranged from 11 months to 11 years; the products incriminated included the following: tripelennamine (Pyribenzamine), wafarin, diphenhydramine (Benadril), kerosene, white shoe polish, hair dye, Humphrey's Pills, merbromin (Mercurochrome), a preparation containing Bellafoline, Gynergen, and phenlyethylbarbiturate (Bellergal Tablets), phenobarbital, acetylsalicylic acid (Aspirin),

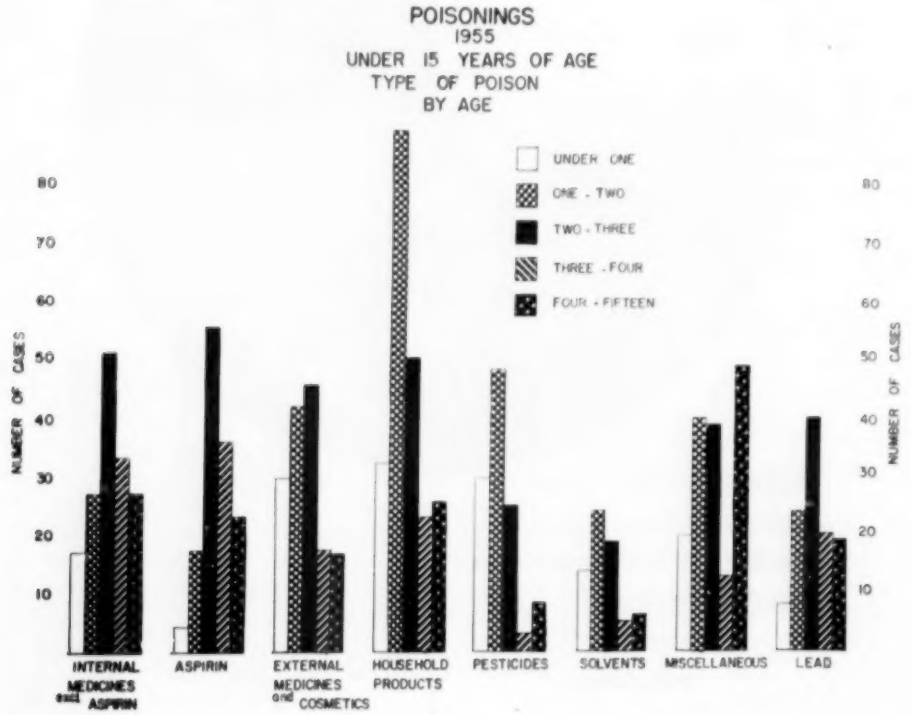

Figure 9

TABLE 5.—*Acetylsalicylic Acid Poisonings with Regard to Age and Season*

Month	Age, Yr. Under 1	1	2	3	4	5-9	10-14	15-19	Over 19	Child Age Unknown	Adult Age Unknown	Total
1955												
March-April		1	7	1				3				12
May	1		3	2				1				7
June			3					4				7
July		2	4	5	3	1		5				20
Aug.			5	6	2	1		1	3			18
Sept.		3	5	1				1	3			13
Oct.	1	1	6	5					3		1	17
Nov.		4	7	7	3		1	1	7			30
Dec.	1	7	13	10	4	4	2	2	5			48
1956												
Jan.	1	3	14	7	1		2	1	5	1		35
Feb. 1-Feb. 15		2	8	9	1		1	2	7			30
Total	4	23	75	53	14	6	6	21	33	1	1	237

diethylstilbestrol (Stilbestrol), and a mixture of ammonia and alcohol. Injurious agents were obtained in open places such as tables, shelves, floor, parents' pocket book, etc.

Changes and Variations by Etiology of Poisoning and Age (Table 7, Fig. 9).—Ages 1 and 2 years are the most hazardous and are practically tied for first place. Together they are responsible for 55% of all accidental poisonings in children under 15 years.

The under-one-year and age-4 groups are tied for second place with 13.7% of all poisonings each, or a combined total of 27.5%. Thus the first 4 years of life exclusive of the "unknown age" contribute 82.5% of all accidental poisonings in children under 15, and this group is thus the most vulnerable.

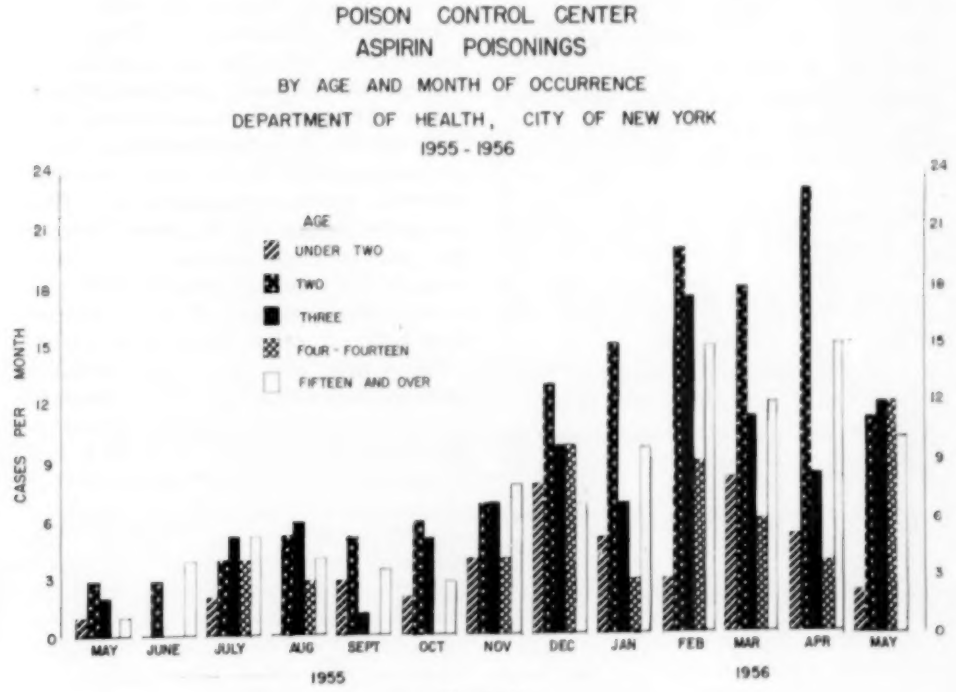

Figure 10

Internal and External Medicines: Exclusive of the miscellaneous category these were together responsible for 40% of the total reported poisonings in the under-15-year group, with acetylsalicylic acid as the chief offender.

Acetylsalicylic Acid Intoxication (Table 5, Fig. 10): Two hundred and thirty-seven (237) acetylsalicylic acid poisonings were reported to the Poison Control Center in its first nine months of operation. The highest incidence occurred at age 2 years accounting for nearly one-third of the total. Age 3 years followed closely behind with an incidence of 22%. Thus children at these two ages were responsible for 55% of the total. Three fatalities in children were also included in this series.

It may be well to cite one fatal case in detail of a 2-year-old white girl.

The mother took two tablets of a 0.32-gm. (5-grain) brand of acetylsalicylic acid and then put the bottle on the table. The 2-year-old child climbed on a chair, obtained the bottle of acetylsalicylic acid and ingested twenty-five 0.32-gm. tablets. Though the child was at first asymptomatic, she was immediately taken to a hospital where emergency treatment was administered and the child was kept for observation. After several hours the child became listless and stuporous and manifested signs of salicylate intoxication. The urine showed a 4+ acetone. In spite of heroic therapy the child died 13 hours after admission to the hospital.

Lead Poisoning (Table 6): One hundred ten (110) lead poisonings were reported in 1955. The highest incidence was at age 2 years, about 43% of the total. Ages 1 and 3 years tied for second place with a combined total of 40%. Ages 1 to 3 contributed 83% of the total number. Eighteen (18) fatalities, or a case fatality of 16.3%, were registered in this group.

The incidence of lead poisonings and fatalities were significantly higher in the nonwhite population. It is believed to be related more to environmental conditions, such as old housing, peeling of plaster from walls and window sills, rather than to inherent constitutional differences. It may be observed that no incident occurred in a child above 11 years of age, and no fatality was reported in persons over 5 years of age.

The seasonal distribution is also of interest. The four summer months (June through September) contributed nearly 60% of the cases.

Confirmed epidemiological investigations on the 110 lead poisonings disclosed that these were chiefly due to ingestion of wall plaster and paint from window sills.

Household Preparations: These substances contributed 19% of accidental poisonings; bleaches were the chief offenders (5%). The pesticides accounted for 10%, and cosmetics and "external drugs" were responsible for 5% of the total. Turpentine and other solvents contributed 6%. Thus acetylsalicylic acid, lead, cosmetics, bleaches, lye, pesticides, and solvents were together responsible for 50% of all occurrences. This is very pertinent, since it clearly indicates that 50% of all accidental poisonings in children could have been easily eliminated if the necessary elementary precautions were

TABLE 6.—*Lead Poisoning Incidents and Deaths in Children with Regard to Age and Sex, 1955*

Age, Yr.	Cases			Deaths			Case Fatality, %
	Boys	Girls	Total	Boys	Girls	Total	
1	15	7	22	1	1	2	9.0
2	27	20	47	7	5	12	25.5
3	14	8	22	2	0	2	9.0
4	8	4	12	1	0	1	8.3
5	2	3	5	0	1	1	25.0
6	1	0	1	0	0	0	0.0
11	1	0	1	0	0	0	0.0
Total	68	42	110	11	7	18	16.3

Sixty-nine of the occurrences were in white children, the vast majority of Puerto Rican extraction.
Twelve of them (17%) were fatal. Forty-one incidents occurred in colored children with six fatalities (15%).

Figure 11

observed in the handling and storage of these substances.

Relation of Age to Injurious Agent and Environment.—The "under-one" and "one-year" age groups suffered mainly from "household preparations," external medications, solvents, bleaches, petroleum distillates, and pesticides. At the age of one year or less a child is still unable to climb and to move about freely, and hence he is a victim of unsafe exposure to articles and substances which are available and easily reached at low levels, such as the floor, a low shelf, under the sink, etc. The highest frequency of poisonings at age 2 and 3, however, is due to "internal medications," or products which are usually stored at higher levels but which can be reached by climbing. Thus the number and kind of poisonings are directly related to a child's stage of growth and development and the frequency of exposure to unsafe agents and an unsafe environment. With advancing age, at 4 and above, the child becomes more cautious because of previous unhappy experiences and the number of poisonings markedly diminish.

The changes and variations by type of poisoning and age are of great epidemiological significance. They clearly demonstrate the relationship of the agent host and environment and their interaction in the causation of an accident and demonstrate clearly how these could be manipulated to avert occurrences.

Other interesting material in this study indicates that many injurious agents involved in poisonings were *not* in their original containers. This was particularly true of pesticides, bleaches, petroleum distillates, and solvents. Household utensils such as coffee cans, drinking glasses, milk bottles, dinner plates, Pepsi-Cola bottles, mayonnaise jars, cups, and saucers were frequently used for their storage. In addition these substances were then placed in open, easily accessible places within reach of young children.

Preventability

A careful analysis of each accident indicated that 98% of accidental poisonings were preventable.

TABLE 7.—*Poisonings with Regard to Age, 1955*

Type of Poison	Age, Yr.													Total
	Under 1	1-2	2-3	3-4	4-5	5-9	10-14	15-19	Over 19	Child's Age Unknown	Adult Age Unknwon	Age Unknown	Total Chief Offenders	
Total internal medicines	21	46	107	70	22	18	11	33	1,108	3	134	27		1,600
Barbiturates	3	6	7	4	0	6	4	10	717	0	107	18	882	
Acetylsalicylic acid	4	18	56	37	14	6	3	6	37	0	1	0	182	
Total external medicines	16	22	34	13	4	7	4	6	123	1	5	7		242
Iodine	1	0	3	0	0	1	1	3	55	0	0	1	65	
Potassium permang.	0	2	9	5	0	1	0	1	10	0	0	0	28	
Total cosmetics*	14	20	12	5	2	0	0	2	15	1	2	1		74
Total household preparations	32	89	50	22	15	6	5	18	104	7	3	8		359
Chlorine Bl.	6	22	17	8	4	3	3	12	37	0	1	0	113	
Furn. Pol.	9	12	1	1	0	0	0	0	2	0	0	0	25	
Pine Oil	4	5	6	3	2	2	0	1	5	1	0	0	29	
Lye	1	4	10	2	7	1	0	1	13	1	0	1	41	
Total Solvents	13	24	19	5	1	5	0	1	22	1	1	6		98
Kerosene	3	2	5	1	1	0	0	0	1	1	0	0	14	
Turpentine	4	9	7	0	0	3	0	1	4	0	0	2	30	
Benzine	4	6	6	3	0	0	0	0	3	0	0	0	22	
Total rodenticides	8	14	7	1	1	0	0	1	16	0	1	0		49
Total insecticides	22	34	18	2	4	3	0	4	25	1	0	1		114
Chlorophenothane (DDT)														
Moth Balls														
Total Miscellaneous	28	63	79	33	16	35	17	1	56	18	14	12		372
Shoe polish														
Lead														
Total all poisonings	154	312	326	151	65	74	37	66	1,469	32	160	62		2,908

* (Cosmetics) deodorant, hair bleach, color tints, shampoo, perfume, and cologne, skin lotion, mascara, liquid make-up.

Value of Home Visits

A careful analysis of the record indicates that family reaction to visit was good in 98% of the cases and that the public health nurse was definitely able to help the family in 97% of the cases with other problems. The public health nurse was selected to do home visiting in cases involving children under 16 for the following reasons:

1. To obtain pertinent data and facts about an accident, a home visit by an experienced observer is vital.

2. Because of the nurse's intimate knowledge of the geographic area involved, its inhabitants, their cultural and social characteristics, home conditions, her previous experiences with the families, because of her training and experience in establishing easy liaison with families, she was considered the most logical person to make the epidemiological investigations.

3. It was also believed and the belief was amply substantiated that the nurse would gain easy access into homes. Families have long been sensitized to accept home visits from nurses into their homes more readily than from any other health and welfare worker.

How Did Families Respond?

Parents and other members of the family were very cooperative and ready and willing to relate the facts concerning the episode, to unfold their anxieties, to provide factual data, and, above all, to receive aid and guidance not only about safety, the prevention of future occurrences, but also about health in general.

It proved an excellent device for case finding and referrals to appropriate health agencies. It may be well to cite an actual case taken at random from the last report received at this writing.

The case involved a 2-year-old boy who ingested 43 gm. (1½ oz.) of paregoric which his older 3½-year-old sister put in a nursing bottle and gave to the patient.

In addition to the problems pertaining to the poisoning, the nurse relates under the heading, "Were any other health problems noted?" "Mother due to deliver fifth child this month. Still not under medical care. Importance of medical supervision during pregnancy discussed. Mother states she dislikes being examined as reason for non-attendance for prenatal care."

"What was nurse able to do on home visit?" "Mother was cooperative and gave information freely. Discussed Accident Prevention; to keep drugs out of reach of children. Importance of medical supervision during pregnancy, infancy and preschool years. Discussed with mother the need to take preschool children for well child supervision. Explained the child health services."

Reports similar to the foregoing are received with great regularity. Since it is felt that attitudes and practices will change only to the extent that persons and families are convinced of the need for such change, it is evident that the public health nurses' visits are eminently successful.

Comment

Accidents are not unpredictable. With a certain constellation of circumstances, an injurious agent, a susceptible host, and an unsafe environment, an accidental occurrence will inevitably result. The large toll of life and disabling injuries resulting from accidents constitutes medical and public health problems of the greatest magnitude. Much still remains in the realm of the unknown which must be identified and determined. A considerable body of knowledge already exists, however, which if more widely applied would greatly contribute to the control of accidents. Several important facts emerge from the studies herein reported.

1. Accidents are commoner in the first 4 years of life.

2. The boy is more susceptible than the girl.

3. Falls and burns are the commonest accidents encountered.

4. Chemical poisonings are in direct proportion to availability and accessibility; thus the more commonly used drugs and household preparations cause the highest number of poisonings.

TABLE 8.—*Accident Fatality Follow-Up Study in Children Under Six, New York City Department of Health, 1953*
Type of Accident and District of Residence

	Total	Accident Rate per 10,000 Population*	Traffic	Poison	Falls	Other	Burns	Suffocation	Submersion
New York City	185	2.4†	36	19	42	6	26	48	8
Manhattan	66	4.1	10	6	22	4	9	12	3
Central Harlem	14	5.5‡	5	1	3	1	2	2	--
East Harlem	19	7.5‡	2	--	9	--	2	5	1
Kips Bay-Yorkville	2	1.4	--	--	1	1	--	--	--
Lower East Side	7	2.1	1	1	2	--	2	1	--
Lower West Side	5	2.4	--	--	1	2	--	1	1
Riverside	18	10.0‡	2	4	5	--	3	3	1
Washington Heights	1	.4	1	--	1	--	--	--	--
Bronx	20	1.4	3	1	4	--	6	6	--
Fordham-Riverdale	1	.5	--	--	1	--	--	--	--
Morrisania	6	2.1	--	--	2	--	1	3	--
Mott Haven	7	3.0‡	1	1	1	--	4	--	--
Pelham Bay	--	.0	--	--	--	--	--	--	--
Tremont	2	.8	1	--	--	--	--	1	--
Westchester	4	1.4	1	--	--	--	1	2	--
Brooklyn	62	2.1	11	12	9	1	7	19	3
Bay Ridge	4	1.3	1	--	--	--	--	3	--
Bedford	8	2.6	--	3	1	--	1	2	1
Brownsville	7	2.2	1	1	1	1	--	3	--
Bushwick	1	.4	--	1	--	--	--	--	--
Flatbush	3	.6	--	1	1	--	--	1	--
Fort Greene	11	4.3‡	1	3	2	--	--	4	1
Gravesend	5	1.7	2	--	--	--	1	2	--
Red Hook-Gowanus	10	5.4‡	1	2	2	--	2	2	1
Sunset Park	5	2.2	3	--	1	--	--	1	--
Williamsburg-Grpt.	8	3.3‡	2	1	1	--	3	1	--
Queens	21	1.3	7	--	4	--	2	6	1
Astoria-L.I.C.	3	1.1	2	--	1	--	--	--	--
Corona	3	1.4	1	--	--	--	--	2	--
Flushing	3	.8	1	--	1	--	--	1	--
Jamaica East	2	.8	--	--	--	--	2	--	--
Jamaica West	5	1.8	1	--	1	--	1	1	1
Maspeth-For. Hills	5	2.1	2	--	1	--	--	2	--
Richmond	6	2.7	1	--	1	--	--	4	--
Non-resident	6		4	--	1	1	--	--	--
Residence Unknown	4		--	--	1	--	1	1	1

* Based on Census of 1950.
† Rate based on 175 resident deaths is 2.3.
‡ Poor socioeconomic area.

5. While no ethnic, social, or religious group is exempt, an inverse relationship exists, with socioeconomic conditions being higher in the nonwhite population and in the low socioeconomic level.

6. The kitchen is the most dangerous place and the bedroom is the next hazardous place in the home.

7. Lack of adult supervision is a deciding contributory factor.

8. Ignorance rather than carelessness was a common finding.

Socioeconomic Influences

Fifty-four per cent of families where fatal accidents occurred were receiving free direct Health Department services. This is more than double the percentage which prevails in the citywide population.

An analysis of all fatal accidents by district of residence (Table 8) discloses that the citywide rate was 2.4 per 10,000 population. The highest rates and excessive numbers, however, were obtained in seven districts of poor socioeconomic areas where housing conditions are poor and overcrowding prevails. These districts also contain a large segment of nonwhites.

How Can the Problem Be Solved?

The problem is complex, perplexing, and enormously difficult, but it can be solved. A vigorous unified battle must be waged on all fronts. It requires a multidisciplined and collective team effort. Medicine, pharmacy, pharmacology, nursing, industry, engineering, chemistry, law, and education, and indeed the entire community must work

harmoniously and collectively toward its effective solution. The control program must be based upon sound epidemiological principles. It is strongly believed that treatment is of secondary importance, but the control and total prevention of accidents are crucial.

Since accidents like disease conditions are not due to a single cause but to a variety of conditions and causes, a multidisciplinary approach is essential.

The Physician and Accident Control

The medical profession has a grave responsibility and a distinct obligation for a contribution to the fullest possible extent to the accident prevention problem.

Practicing physicians have an enviable record of achievement with regard to prevention of communicable and infectious diseases. There is no reason why they should be less successful in the field of accident prevention. Health education is the most potent single factor in any control program, but it is particularly effective in accident prevention.

Practicing physicians have engaged in health guidance and counselling to families for many years, and they can thus easily incorporate into their daily practice and medical armamentarium the principles of home safety and accident prevention. The family physician and pediatrician have ample knowledge of family background, child's stage of growth and development, parent-child relationship, habits and attitudes, and physical, biological, and social environment. They are thus in a most strategic position to provide anticipatory guidance and counselling to parents on how to avert accidents which are most likely to occur at a given age level or stage of development.

It is not recommended that a child's normal play activities be curbed and that he be prevented from exploring and learning his environment. It is advocated, however, that he be better protected, supervised, disciplined, and that his dynamism be more appropriately guided.

The physician must become better acquainted and acquire a greater understanding of the influencing and determining factors and the psychodynamics of accident occurrence. As a matter of fact, the physician's education and involvement in the accident prevention program should logically begin at the undergraduate level. Appropriate emphasis should be given to this problem in the medical school curriculum. (Parenthetically, this also holds true for schools of nursing and pharmacy).

Through daily contact with families and children, the physician is in a most strategic position to provide health education on safety during his regular visits in the home for the care of the sick. As an experienced observer he may also notice any potential hazards and unsafe conditions in and about the home and advise families about the indicated corrective measures.

Considerable health education, guidance, and counselling can also be provided during office visits. He can administer to children not only immunizations against communicable diseases but also a safety vaccine of education which is painless but effective, administered to parents and children alike against accidents. The physician must inculcate in his patients a desire for home safety and accident prevention.

The physician should also inquire about a history of accidents in the same manner as he inquires about past illnesses. As a matter of fact, this query should be a regular part of his routine medical record.

The physician's waiting room should include reliable health education material (devoid of overdramatization) about the accident problem and how families can aid in the prevention of accidents.

Prescriptions for drugs should be written legibly and meticulously. Written instructions shall be given as to type of medication, amount, dosage, when drug is to be administered; and on the importance of keeping the medication entirely out of reach of children, in the original container, under lock and key. The dangers of self-medication should be emphasized. The physician should also instruct his office nurse on safe habits and attitudes and about the dangers of dis-

pensing "samples." The physician also has a rare opportunity in orienting pharmacists on the dangers of selling drugs and medication over the counter and on the need to tell their clientele whenever drugs and household preparations are dispensed to keep them in the original container and away from the reach of children.

As a community educator he must become scrupulously safety minded. "Accidents" under his care should be reported promptly and in careful detail to the local Health Department. Sound preventive programs can only be formulated on the basis of facts obtained through such epidemiological reporting and analysis.

Patient participation in the prevention program by means of home check lists, etc., also pays handsome dividends.

The physician should also advise on the need for safe and well-supervised recreational activities in public playgrounds and other play areas.

As a leader in the community he can also motivate interested groups, such as parent-teacher associations, health councils, 4-H clubs, the Scouts, and numerous other organizations, in initiating safety and accident prevention programs.

The primary focus of the medical profession now must be on health rather than disease. The practice of preventive medicine is rightly in the domain of the practicing physician and particularly of the pediatrician.

Accident prevention is a worthy challenge to physicians the world over.

Summary and Conclusions

Data are presented on 3000 nonfatal accidents in children under supervision in New York City Child Health Stations (1951-1955), and on 1151 accidental poisonings (fatal and nonfatal) reported to the Poison Control Center in 1955.

Accidents are responsible for more deaths in the preschool child than the 10 leading communicable diseases combined.

Falls and burns are the primary offenders in the accident group and acetylsalicylic acid (aspirin) and lead are the chief offenders in the accidental poisonings.

The boy is more susceptible than the girl, and the nonwhite is more vulnerable than the white. The higher susceptibility in the nonwhite is believed to be a reflection of socioeconomic conditions such as overcrowding, poor housing, etc., rather than of inherent and constitutional differences.

Accidents follow an epidemiologic pattern like disease processes and are amenable to control measures. Attention must be focused on the most vulnerable groups with high attack rates and on injurious agents most commonly incriminated.

Approximately 95% of the accidents in this study were judged preventable.

Type of accident is intimately associated with the child's stage of growth and development.

Accident proneness was not observed as a pattern. This observation does not confirm findings of other observers.

A dynamic, imaginative, daring, and comprehensive control program is indicated, preventive measures to be based on facts obtained in epidemiological investigations.

Accident control is a medicosocial community-wide program. It is multidisciplined and multifacetted, and all skills must play a part in its effective solution.

Prevention is crucial and education is the keystone of the program.

The role of the practicing physician as a key person is outlined. Further epidemiological investigative research is needed and particularly about the emotional and human factors and the psychodynamics involved.

Harry Raybin, Technical Director of the Poison Control Center, and Herbert Rich, Norman Skop, Miss Frieda Greenstein, and Mrs. Florence Rich aided with the compilation of the statistical data, and physicians in child health stations reported nonfatal accidents, and public health nurses made the home visits.

Department of Health, 125 Worth St.

REFERENCES

1. Accident Facts, Annual Publication, Chicago, National Safety Council, 1955.

2. Gordon, J. E.: Epidemiology of Accidents, Am. J. Pub. Health 39:504-515 (April) 1949.

3. Roberts, H. L., and Gordon, J. E.: Home Accidents in Massachusetts: Study in Epidemiology of Trauma, New England J. Med. 241: 435-441 (Sept. 22) 1949.

4. Roberts, H. L.: A Community Surveys Its Home Accidents, Am. J. Pub. Health 41:1118-1121 (Sept.) 1951.

5. Jacobziner, H., and Rich, H.: Home Safety and Accident Prevention in a Child Health Conference, Am. J. Pub. Health 44:83-93 (Jan.) 1954.

6. Jacobziner, H.; Heely, I. P., and Rich, H.: Accident Fatality Follow-Up Study in Children Under 6, GP 13:88-95 (Feb.) 1956.

7. Jacobziner, H.: Task Force—Accident Control, New York J. Med. 56:1923-1927 (June 15) 1956.

8. Bain, K.: Death Due to Accidental Poisoning in Young Children, J. Pediat. 44:616-623 (June) 1954.

9. Swinscow, D.: Accidental Poisoning of Young Children, Arch. Dis. Childhood 28:26-29 (Feb.) 1953.

10. Press, E., and Mellins, R. B.: A Poisoning Control Program, Am. J. Pub. Health 44: 1515-1525 (Dec.) 1954.

11. Jacobziner, H.: Chemical Poisonings in Children, J. A. M. A., to be published.

12. Dunbar, F.: Mind and Body: Psychosomatic Medicine, New York, Random House, Inc., 1947.

13. Bakwin, R. M., and Bakwin, H.: Accident Proneness, J. Pediat. 32:749-752 (June) 1948.

14. Fuller, E. M.: Injury-Prone Children, Am. J. Orthopsychiat. 18:708-723 (Oct.) 1948.

Studies of Babies Born at High Altitude

I. Relation of Altitude to Birth Weight

JOHN A. LICHTY, M.D.; ROSALIND Y. TING, M.D., M.P.H.; PAUL D. BRUNS, M.D., and ELIZABETH DYAR, Ph.D., Denver

As a part of Colorado's Premature Infant Program, the State Department of Public Health obtained the incidence of prematurity by counties in the state. There was considerable variation among the counties, but one (Lake County) had a much higher incidence than any of the others and, hence, has been the object of more intensive study. Table 1 shows a five-year picture of this county compared with the state average for prematurity and neonatal mortality. Although the incidence of prematurity by birth weight was 30.8%, three times the state average, the neonatal mortality was not proportionately high. The physicians practicing in this area expressed the opinion that babies born there were often small but not premature. The fact that the residents of this county live at an altitude of 10,000-11,000 ft. prompted consideration of the possibility that altitude was responsible for the small babies.

TABLE 1.—*Prematurity and Neonatal Mortality Rates, Colorado and Lake County Place of Residence*

Year	Live Births Lake County	% Live Births Premature*		Neonatal Death Rates*	
		Lake	Colo.	Lake	Colo.
1949	223	45	10	84	24
1950	185	30	11	43	23
1951	223	28	10	18	24
1952	271	24	11	30	22
1953	304	27	10	33	24
Five-yr. av.	241.2	30.8	10.4	41.6	23.4

* Per cent of live births with weights of 2500 gm. (five and one-half lb.) or under and deaths under one month of age per 1000 live births.

In this study detailed medical information was obtained from 180 mothers with 615 newborns in this county, using interviews by a physician and written questionnaries. At the same time, the Home Economics Section of Colorado Agricultural and Mechanical College obtained "one-day recall" dietary data and socioeconomic information from the mothers by similar means. Available records from the Health Department and St. Vincent's Hospital in Lake County were also used.

The first step was a study of recorded weights of 577 babies born in St. Vincent's Hospital in Lake County over the three-year period 1949-1951 inclusive, together with those of 633 randomly selected babies born at Colorado General Hospital and 609 born at Denver General Hospital during the same period. Comparison of average

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Departments of Pediatrics and Obstetrics and Gynecology, University of Colorado School of Medicine; Colorado State Department of Public Health, and Home Economics Section, Colorado Agricultural and Mechanical College.

The Child Research Council of Denver; the physicians of the Lake County Medical Society; the Hospital Staff, St. Vincent's Hospital, Leadville; and the Statistical Services, Department of Health and Hospitals, City and County of Denver, provided consultation and assistance in these studies.

TABLE 2.—*Distribution of Live Birth Weights in Different Geographic Areas*

Weight Group, Gm.	U.S.A.[1]	Baltimore[2]	Denver[3]	Cripple Creek	Lake County
	3300 NB*	9523 NB	10566 NB	244 NB	377 NB
1000 or less	0.5%	0.6%	0.7%	0.4%	0.9%
1001–1500	0.6	0.7	0.8	1.6	3.3
1501–2000	1.4	1.8	1.9	5.3	13.7
2001–2500	4.9	5.8	8.3	10.6	30.4
2501–3000	18.1	23.3	27.4	31.4	32.2
3001–3500	37.7	39.4	40.8	39.6	17.2
3501–4000	27.1	21.8	16.7	9.0	2.4
4001–4500	7.7	5.5	3.0	2.0	0.0
4501 and more	2.1	1.1	0.3	0.0	0.0

* Newborns.
1. Weight at Birth and Its Effect on Survival of Newborn in U.S.A., Early 1950, Vital Statistics—Special Reports 39:9, National Office Vital Statistics, July, 1954.
2. Taback, M.: Birth Weight and Length of Gestation with Relation to Prematurity, J. A. M. A., 146:897 (July) 1951.
3. 1953 Report, Office of Statistical Services, Denver Department of Health and Hospitals.

birth weights showed that the Lake County newborns weighed 380 gm. less than the two groups of infants born to medical indigents at the Denver hospitals used in the study. In Table 2 and Figure 2 the percentage distribution of Lake County birth weights is shown, using 500-gm. intervals; for comparison, similar data for the whole United States and for Baltimore, Md., Denver County, and Cripple Creek, Colo., are included. Denver's altitude is about 5000 ft. and that of Cripple Creek is about 9000 ft. The distribution curve for Denver newborns agrees quite closely with those (not shown in the chart) for the two University Hospitals mentioned above. The data for Cripple Creek are in closer agreement with those of Denver than those of Lake County.

Boder[1] has suggested that altitude does influence the mean birth weight of the Mexican babies she has studied. In Table 3 her published data are shown, together with Lake County and Denver averages. The gradual increase in weight of newborns with the decrease in altitude of birthplace is

Fig. 1.—Leadville, Colo., 10,000 feet and Mt. Massive, 14,418 feet.

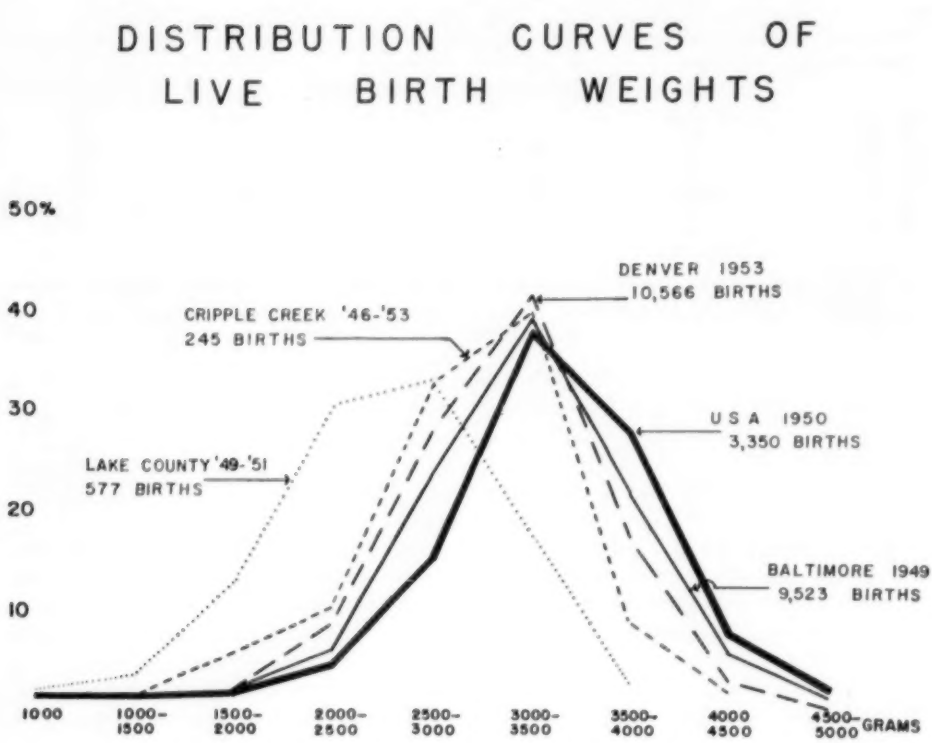


Figure 2

TABLE 3.—*Relation of Newborn Weight to Altitude* *

Place	Altitude, Ft.	Mean Birth Wt., Gm.
(Lake County, Colo., 1949-1951)	(10,000-11,000)	(2655)
Mexico City	7,000	2992
(Denver County, Colo., 1953)	(5,280)	(3035)
Guadalajara, Mexico	2,200	3219
Mazatlan, Mexico	sea level	3277
Los Angeles	740	3443

* Elena Boder, personal communication to Arthur Parmelee for table in "Management of Newborn," Year Book Publishers, Inc., 1952.
(Colorado data).

readily apparent. However, her figures do not include any babies weighing less than 2500 gm., and, hence, the Colorado values are not strictly comparable. No other reference to a relationship of altitude and human birth weight was found.

Since approximately one-third of the population of Lake County is Spanish-American, the factor of race was considered as a possible cause for the small babies. However, comparison of average weights of "Anglo" and "Spanish" infants, born at each of the three hospitals studied, revealed no significant differences.

Because the climate of Lake County is severe, very few people who are not employed live there, and as a result the county has one of the highest per capita incomes in the state. Questionnaire information regarding the dietary habits and socioeconomic index for the people in this high-altitude county failed to reveal any significant differences between that group of mothers who had newborns weighing more than 2500 gm. and the group whose babies weighed 2500 gm. or less. In comparison with the National Research Council's Recommended

TABLE 4.—*Comparison of Diets of 186 Lake County Mothers with Various Levels of NRC Recommended Dietary Allowances* *

Infants	Level of NRC Allowances					
	Below Two-Thirds		Two-Thirds to Full		Full and Over	
	Full-Term Per Cent of Mothers	Premature Per Cent of Mothers	Full-Term Per Cent of Mothers	Premature Per Cent of Mothers	Full-Term Per Cent of Mothers	Premature Per Cent of Mothers
Calories	35	29	39	39	26	32
Protein	10	13	35	23	57	64
Calcium	45	36	22	31	33	33
Iron	27	28	47	39	26	33
Vitamin A	52	58	23	23	25	19
Thiamine	44	39	23	26	33	35
Riboflavin	24	27	34	22	42	51
Niacin	28	29	38	25	34	46
Ascorbic Acid	63	55	10	23	27	22

* Recommended Dietary Allowances revised 1953, National Academy of Sciences, National Research Council Publication No 302, Washington, D. C., for women aged 25 years.
In some cases there was more than one birth per mother between January, 1949, and December, 1951. Therefore, the mothers were counted as many times as there were births (117 full-term and 69 premature births).

Dietary Allowances (1953), Table 4 shows information regarding nine nutrients in the diets of 186 Lake County mothers who had given birth to live infants during 1949-1951. The figures shown are the percentages of mothers whose diets fell within the ranges indicated. Using the "one-day recall" method, no significant differences were found between the intakes of mothers having full-term and those having premature infants. The premature infants are those newborns weighing 2500 gm. or less at birth. Also, routine chemical analyses of Lake County water samples by the Colorado State Department of Public Health showed no abnormalities.

The experimental work of Ingalls [19] has suggested that the hypoxia of simulated high-altitude conditions is associated with congenital defects. Hence, the incidence of such defects in Lake County newborns was compared with those of Denver, New York City, and upstate New York. Table 5 shows that there were no significant differences. This finding tends to support the statement of practicing physicians in Lake County that the babies are often small but not otherwise abnormal. Possibly the generally accepted birth weight of 2500 gm. is not appropriate for distinguishing between full-term and premature infants in this community.

TABLE 5.—*Prevalence of Congenital Defects*

Lake County, 1949–1951 (questionnaires)	1.3% (8/614)
Denver, 1951 (birth certificates) [1]	1.6%
New York City, 1951 (birth certificates) [2]	0.9%
New York State, 1940–1942 (birth certificates) [3] (outside New York City)	1.1%

1. Sanchez, J. J., personal communication to the authors.
2. Wallace, H. M.; Baumgartner, L., and Rich, H.: Congenital Malformations and Birth Injuries in New York City, Pediatrics 12:525 (Nov.) 1953.
3. DePorte, J. V., and Parkhurst, E.: Congenital Malformations and Birth Injuries Among Children Born in New York State, Outside of New York City, in 1940-1942, New York J. Med. 45:1097 (May 15) 1945.

Summary

The incidence of prematurity, by birth weight, for a high-altitude county in Colorado was found to be 30.8%, in contrast to the state average of 10.4%.

The neonatal mortality for this county was not proportionately high.

A comparison of average birth weights for newborns of this county and a comparable group of newborns in Denver shows that the high-altitude babies are about ¼ lb. lighter than the Denver babies.

Comparison of such factors as race and dietary intake for mothers with full-term and mothers with "premature" infants, born in this county, revealed no significant differences.

The incidence of congenital defects in the newborns of this county was approximately the same as those reported for Denver, Colorado, and New York State.

II. Measurement of Birth Weight, Body Length, and Head Size

ROBERT C. HOWARD, M.D.; JOHN A. LICHTY, M.D., and PAUL D. BRUNS, M.D., Denver

As indicated in a previous report,[2] studies based on hospital records and personal interviews with mothers for one of Colorado's high altitude counties revealed an unusually high incidence of babies weighing 2500 gm. or less at birth (Part I). For the years 1949-1951 inclusive, the average weight of all (577) these Lake County newborns was 380 gm. less than that of a randomly selected group of medically indigent babies born at the University of Colorado Hospitals, in Denver. It was not possible to explain this finding on the basis of ethnic groups or gross dietary deficiencies. Since Lake County residents live at an altitude of 10,000-11,000 ft. above sea level, while Denver has approximately half that elevation, consideration was given to the possibility that altitude influenced the size of Lake County newborns.

The present paper represents an extension of the Lake County newborn studies, consisting of measurements of weight, body length, and head size made shortly after delivery.

Materials and Methods

One hundred and forty-five deliveries, occurring between April 1 and Dec. 30, 1955, were attended by one of us (R. C. H.) to obtain measurements on 142 live-born infants. These were all single births. Infant measurements were made with calibrated baby scales, calipers (for head size), and an infant measuring board equipped with a fixed centimeter scale and sliding footpiece. Length of gestation was computed from the first day of the last normal menstrual period. The record of previous pregnancies, menstrual and health histories was obtained by personal interviews and from St. Vincent Hospital records at Leadville, Lake County, Colo.

One hundred eleven of the one hundred forty-two infants measured were born by spontaneous delivery. There were 10 inductions for medical reasons, 16 elective inductions, and 4 cesarean sections. One self-induced abortion resulted in a neonatal death. Mothers who were given only oral medications to hasten the onset of labor were not included in the "induced" group. Inductions performed because of "overterm fetus" or "threatened disproportion" were considered as elective. Induction was usually initiated by artificial rupture of the membranes and/or the use of oxytocin injection U. S. P. (Pitocin).

This study was supported by a research grant from Playtex Park Research Institute.

TABLE 6.—*Distribution of Live Birth Weights in Denver and Lake Counties*

Weight Group, Gm.	Denver 1953 10,566 NB*	Lake County 1955	
		111 Spont. Births	142 Unselected NB†
1000 or less	0.7%	0.0%	0.7%
1001–1500	0.8	0.0	0.0
1501–2000	1.9	3.6	2.8
2001–2500	8.3	13.4	13.3
2501–3000	27.4	44.7	42.7
3001–3500	40.8	32.1	32.2
3501–4000	16.7	6.2	7.7
4001–4500	3.0	0.0	0.7
4501 or over	0.3	0.0	0.0

* Newborns.
† Includes the 111 spontaneous births.

Results and Interpretations

Table 6 shows the percentage distribution of birth weights of all the 142 Lake County babies studied and of the 111 newborns resulting from spontaneous deliveries. Birth weight data from unselected babies born in Denver are shown for comparison. It can be readily seen that the 1955 Lake County newborns weighed less than those of Denver. On the other hand, the weight distribution curve of the Lake County group shows good agreement with that for the 1949-1951 group of Lake County newborns (Table 2, Part I). Since the great majority of the 1955 newborns resulted from spontaneous deliveries, obstetrical intervention cannot wholly explain their small size.

The estimated gestational age of the Lake County babies, including those from spontaneous and induced deliveries, is shown in Figure 3. Although the numbers are small, the distribution of gestational ages compares well with that of a large series

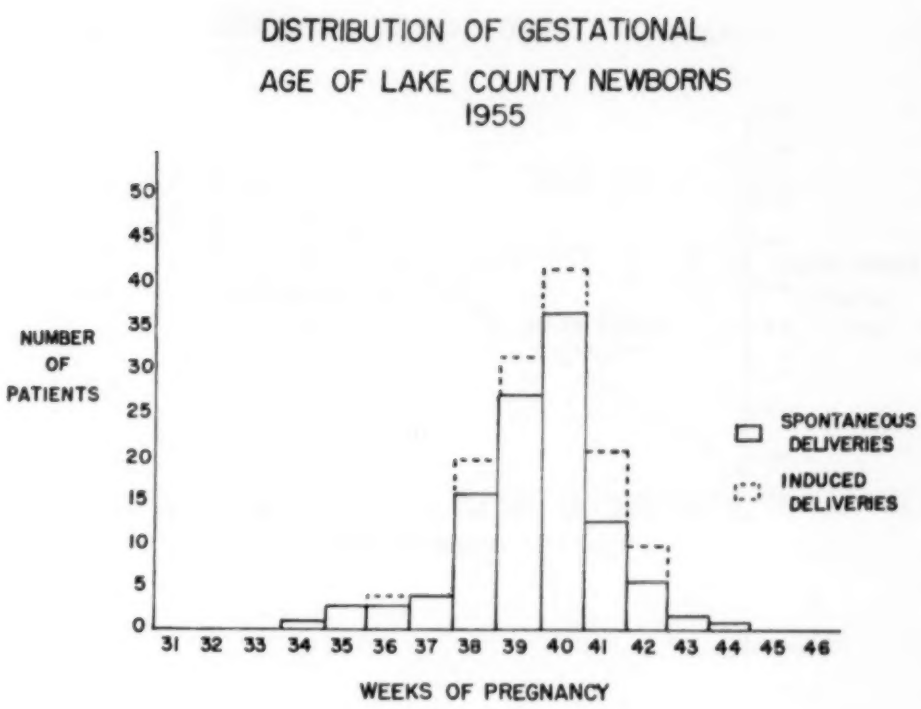


Figure 3

of pregnancies at sea level reported by Taback.[3] Even in the induced-delivery group there is little preponderance of pregnancies with shortened gestational ages.

The values for birth weight, crown-heel length, and biparietal and occipitofrontal skull diameters are plotted against length of gestation in the four scattergraphs of Figures 4A and 4B. For comparison, mean values are shown for similar measurements obtained by Boyd from living and dead babies at the University of Minnesota.[8] Inspection of these graphs shows the consistently reduced body measurements for the majority of the Lake County newborns as compared with a larger group born near sea level. The reduced size of these infants reinforces the observations regarding reduced birth weight for the high-altitude babies studied.

Because a large proportion of the Lake County residents are transients, efforts to compare the weight of infants born to the same mothers before and after moving to Lake County were made in both the previous study (Part I) and the present one. Relying on the mothers' memories for birth weights of previous pregnancies, we obtained pertinent information regarding 120 mothers who had 293 babies before living in Lake County and 261 while living there. The average weights of these respective groups of newborns were 3130 gm. and 2840 gm., a difference of 290 gm. in favor of babies born before the mother moved to Lake County.

Comment

Increasing attention has been given to the subject of high altitude physiology since shortly after the turn of the century, thanks largely to the development of aviation medicine and to the interest of cardiologists. However, there are comparatively few reported studies dealing with reproductive capacity or bearing on the human newborn.

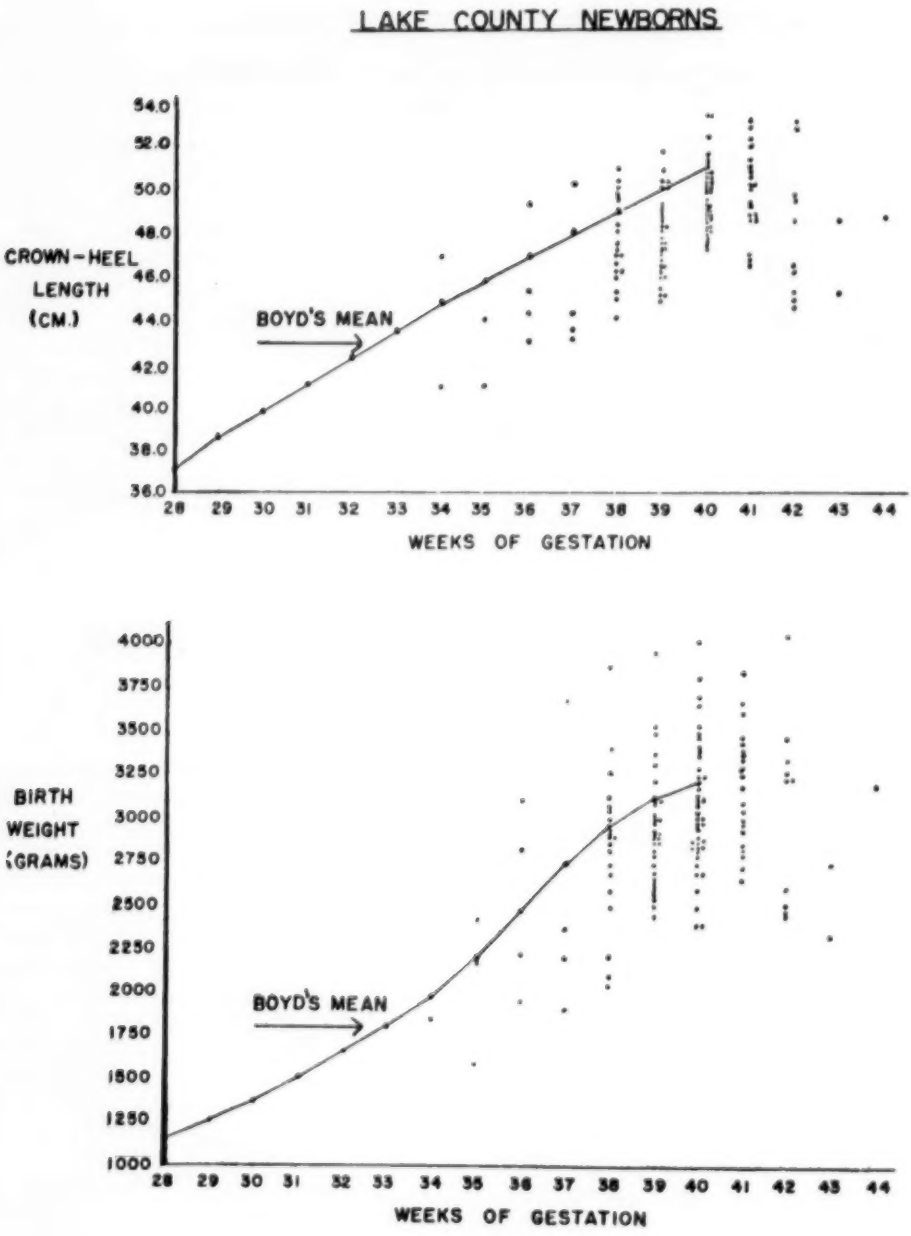
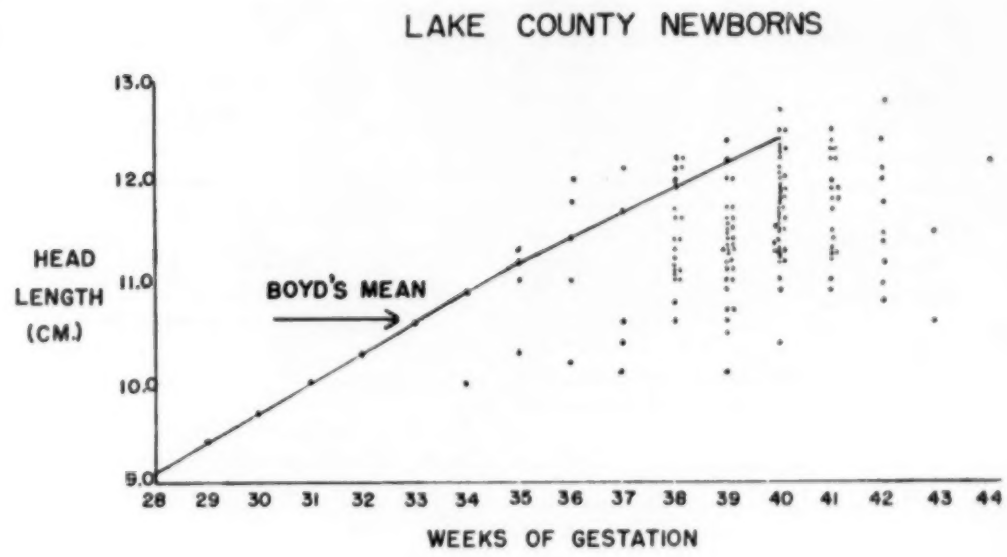


Figure 4A

Monge[4] cites the historian Antonio de la Calancha (1639), who describes the inability to reproduce of the earliest Spanish gold seekers in the high plateau country of Peru (12,000 ft. altitude). By this account, although the Indians continued to reproduce prolifically, it was 53 years after the founding of the city of Potosi before



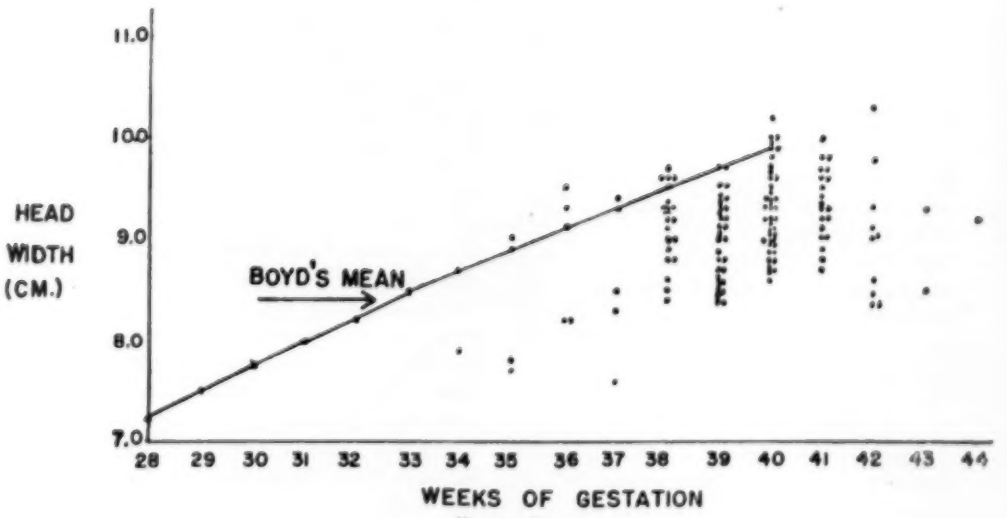


Figure 4B

the first Spaniard was born. Delafield,[5] however, in a personal communication from the Chulec General Hospital at La Oroya, Peru, wrote that conception among Europeans living there seemed to present no problem.

Utilizing albino rats, Moore and Price[6] were unable to show a significant difference in the weights of endocrine and reproductive organs, spermatogenesis, breeding capacity and rate, litter number, or birth weight of young among colonies of animals reared

at elevations of 600, 7500, 9600, and 14,260 ft. Later, Chiodi,[7] of the Institute of High Altitude Biology, Mina Aguilar, Argentina, found an unusually high mortality of rats in the first few days of life at 12,000 ft. Such mortality, apparently due chiefly to hepatic damage, could be eliminated if the rat colony were kept in an atmosphere with oxygen tension similar to that of sea level.

Studying groups of Mexican babies, Boder[1] has advanced the suggestion that an inverse correlation exists between altitude and birth weight. The data from this study tend to substantiate her belief that babies born at high altitudes show somatic reduction.

Summary

Over a nine-month period, measurements of birth weight, body length, and head size were made for 142 newborn infants in Lake County, Colorado.

For 111 spontaneously delivered infants, the average reduction in birth weight compared very closely with that of another series of Lake County newborns described in the previous report (Part I).

The average birth weight of Lake County newborns was from one-half to three-fourths of a pound less than babies born in Denver, in Colorado, or elsewhere in the United States.

The body length and head size of Lake County newborns were likewise reduced as compared with those of babies born elsewhere.

III. Arterial Oxygen Saturation and Hematocrit Values at Birth

ROBERT C. HOWARD, M.D.; PAUL D. BRUNS, M.D., and JOHN A. LICHTY, M.D., Denver

This report represents studies attempting to test the hypothesis that oxygen lack might be one factor influencing the birth weight and size of infants born at an altitude of 10,000-11,000 ft. in Lake County, Colorado. Specific attention was directed to measuring the arterial oxygen saturation of newborns and their mothers and to the infants' circulating erythrocyte mass during the first few days of life. The general plan of the study was to compare the results obtained with those of similar determinations made by Taylor et al.[9] at the University of Colorado Medical Center (altitude 5000 ft.).

Material and Methods

Applying the technique which Taylor had used for use of the Wood-Geraci[10] ear oximeter in studies of arterial oxygen saturation of human infants, measurements were made on the 142 Lake County newborns described in Part II. The oximeter, a single-scale absolute-reading instrument, is a modification of that described by Wood[11] and provides a means for obtaining multiple or continuous arterial oxygen saturation values. The physical basis of the method and its reliability have been discussed by Crehan et al.[12] It involves the differential transmission of light of a specified wavelength by oxyhemoglobin and reduced hemoglobin. The earpiece of the instrument, consisting of a light source and two photoelectric cells, is affixed to the heat-flushed pinna of the intact ear, and the relative light absorption is determined for the two types of hemoglobin in the interposed capillary blood. Readings so obtained are not significantly affected by skin pigmentation, hemoglobin level, or ear thickness.

Oximetric determinations were obtained at delivery from 99 mothers in Lake County. The readings were made before any anesthesia had been administered, but the majority of mothers had received meperidine (Demerol) hydrochloride, 100 mg., and scopolamine, 0.4 mg., within the four hours preceding delivery. All mothers were in good health and had no complications of pregnancy.

This study was supported by a research grant from Playtex Park Research Institute.

The earpiece was then detached from the mother, and determinations were made on the infant as soon as the head was born. With few exceptions the initial reading was obtained at two minutes after birth of the head. Subsequent readings were made at two-minute intervals for the first half-hour or until the oxygen saturation had become stabilized at a value of at least 90%.

The oximeter values in this study were verified periodically by the use of a microchemical method for determining blood oxygen saturation devised by Roughton and Scholander.[13] Analysis of cord vein blood was employed for comparison with the lower oxygen-saturation readings obtained immediately after delivery. Determinations were restricted to those deliveries at which an initial oximeter reading could be obtained and a length of umbilical cord doubly clamped before the baby inspired. For comparisons at higher saturations microgasometric analyses were performed on capillary blood collected anaerobically from a free-flowing sample obtained by a heel prick. Most of the latter comparisons were made on the fifth day of life.

Figure 5 shows the correlation between the oximetric and gasometric determinations of newborn arterial oxygen saturation. With few exceptions there was agreement within 5% at saturations below 80%. Above this level oximeter readings were frequently higher than the corresponding gasometric values. As in the case of Taylor's studies, it was common to obtain readings between 100% and 106%. Also, during the period of blood collections from the heel prick, oximeter readings varied over a range of 10% because of the infant's reactions to the procedure. In all cases, however, the reading at the beginning of the blood-collection time was taken as the value for comparison with the oximeter reading.

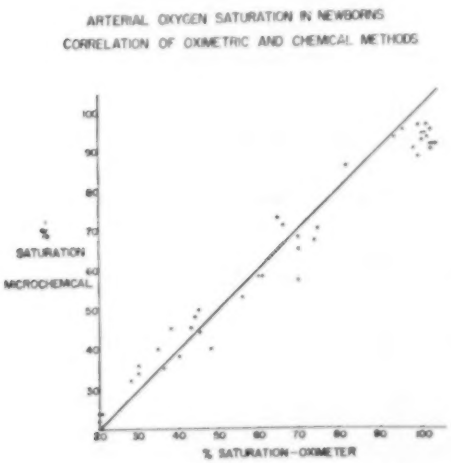

ARTERIAL OXYGEN SATURATION IN NEWBORNS
CORRELATION OF OXIMETRIC AND CHEMICAL METHODS
% SATURATION MICROCHEMICAL
% SATURATION—OXIMETER

Figure 5

Hematocrit determinations were performed in triplicate by the use of a capillary-tube technique using heparinized tubes and a special hematocrit centrifuge. The tubes were spun at 10,000 rpm for five minutes before reading. Hematocrit determinations were made on cord blood and also on capillary blood from a free-flowing heel prick on the fourth or fifth day of life. This method gave a precision of 3% maximum variation between the readings of any two tubes. The general reliability of the method has been tested against the Wintrobe method of hematocrit determinations by Guest and Siler.[14]

Results

The ear oximeter oxygen-saturation values for the group of Lake County mothers varied between 90% and 100%, with a mean value of 95%. These results are within the accepted range of normal for similar determinations at lower altitudes.

From the series of Lake County infants studied, a group of 49 were selected as being most comparable to those used in Taylor's studies in Denver. These babies were normal newborns whose mothers received meperidine hydrochloride and scopolamine within the four hours preceding delivery but received only intermittent trichlorethylene analgesia during labor. In view of Taylor's results, it was considered that the latter could be disregarded as a factor operating to lower the infant's blood oxygen saturation. The mothers were all in good health

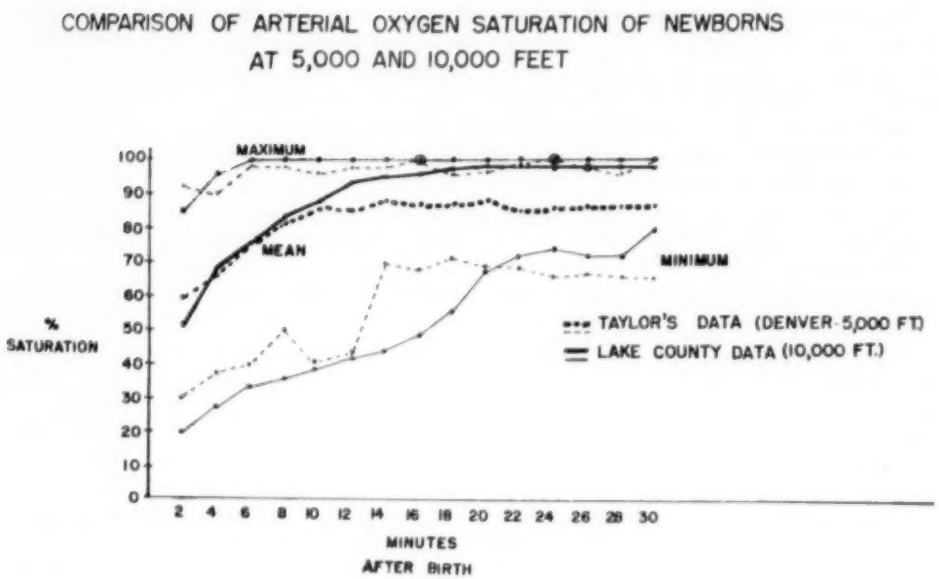


Figure 6

and pregnancies and labors were uncomplicated. Whereas the Denver group of newborns were all "full-term" (birth weight over 2500 gm.), eight of those in the Lake County group weighed 2500 gm. or less at birth.

Figure 6 shows a comparison of the Lake County and Denver infants with respect to mean, maximum, and minimum arterial oxygen saturations at two-minute intervals following delivery, as measured by the oximeter. All readings above 100% were corrected to that value, as was done in Taylor's report. Although the Lake County mean value for the initial reading (two minutes after delivery of the head) was slightly lower than that of the Denver infants, mean saturations from 4 to 10 minutes of life were practically identical for the two groups of newborns. Beyond 10 minutes the average arterial oxygen saturation of the high altitude infants was actually higher than that of the Denver ones.

Regarding hematocrit studies, Table 7 again shows a comparison of data on Lake County newborns with those of two independent groups of Denver infants studied by Mugrage and Andresen.[15] In this instance the agreement is almost exact. However, because these authors used a slightly different technique for hematocrit determinations, an additional group of 30 newborns at Colorado General Hospital was studied by the same technique used for the

TABLE 7.—*Hematocrit Comparisons*

Source	Lake County				Denver		
	Cord Blood		Capillary (4-5 days)				
	Prem.*	Mature	Prem.	Mature	Cord	Cord†	Superficial Vein† (30 min.-19 days)
Number of determinations	22	95	18	92	30	40	30
Maximum	62	76	68	73	64	—	—
Minimum	44	40	52	46	40	—	—
Mean values	53.4	53.4	59.3	57.8	53.0	53.18	54.92

* Birth weight of 2500 gm. or less.
† Mugrage and Andresen.

Lake County newborns. The results of these determinations are also included in Table 7 and again the agreement was extremely good. Certainly there was no evidence of polycythemia in the Lake County newborns.

Comment

The data relating to arterial oxygen saturation presented in this report do not support the hypothesis that an infant born from an uncomplicated pregnancy and delivery at an altitude of 10,000 ft. (barometric pressure 523 mm. Hg) is more hypoxic than one born at a lower altitude. Neither oximeter readings nor gasometric determinations of cord vein blood have shown any significant variations from values for the average newborn. Since such studies, carried out at the time of delivery, might not represent the picture of fetal oxygenation for the entire pregnancy, hematocrit studies of the newborn were made to find out if intrauterine hypoxia might be reflected in an increase in the mass of circulating erythrocytes of these high-altitude infants. This was based on the finding of Walker [16,17,20] that when the placenta is unable to satisfy fetal oxygen requirements compensatory polycythemic adjustments are found in the fetus. No such polycythemia was found in the Lake County babies, as compared with control groups.

Reticulocyte counts might have provided a more sensitive hematologic index of intrauterine hypoxia. Their values at birth, however, vary so widely that a high-altitude series of newborns, much larger than the present one, would have been necessary for meaningful comparisons with normals.

Since anoxia has been implicated in the production of some congenital anomalies,[18,19] the incidence of such in the Lake County series was noted. Of the 142 infants, 6 (4.2%) had the following gross malformations: 2 cases of acyanotic congenital heart disease, one case of tracheoesophageal fistula with esophageal atresia, one of cleft palate and micrognathia (Pierre-Robin syndrome), one case of bilateral inguinal hernia, and one of bilateral microphthalmia with corneal opacity. In none of these cases did questioning of the mother reveal a history of known intrapartum infection, x-irradiation, or obvious dietary or metabolic abnormality. Although the incidence of defects in this series of Lake County newborns is more than three times that reported from the questionnaire studies reported in Part I, the small number of cases involved does not permit any conclusions to be drawn.

Summary

Comparison of arterial oxygen saturations and hematocrit values for a series of infants born at high altitude (10,000 ft.) with similar values for a comparable series of newborns at half that elevation yielded no significant differences.

REFERENCES

1. Boder, E., cited by Parmelee, A. H.: Management of the Newborn, Chicago, Year Book Publishers, Inc., 1952, p. 136.

2. Lichty, J. A.; Ting, R. Y.; Bruns, P. D., and Dyar, E.: Incidence of Prematurity Higher at High Altitude, Abstract, Pub. Health Rep. 70:230, 1955.

3. Taback, M.: Birth Weight and Length of Gestation with Relation to Prematurity, J. A. M. A. 146:897, 1951.

4. Monge, C.: Acclimatization in the Andes: Historical Confirmations of "Climatic Aggression" in the Development of Andean Man, Baltimore, Johns Hopkins Press, 1948.

5. Delafield, R. H., personal communication to the authors.

6. Moore, C. R., and Price, D.: Reproduction at High Altitudes, Anat. Rec. 99:574, 1947.

7. Chiodi, H.: Mortality of Young Rats at Mountain Heights, Foreign Letters, J. A. M. A. 153:162, 1953.

8. Boyd, E.: An Introduction to Human Biology and Anatomy for First Year Medical Students, The Child Research Council of Denver, Colorado, 1952.

9. Taylor, E. S.; von Fumetti, H. H.; Essig, L. L.; Goodman, S. N., and Walker, L. C.: Effects of Demerol and Trichlorethylene on Arterial Oxygen Saturation in the Newborn, Am. J. Obst. & Gynec. 69:348, 1955.

10. Wood, E. H., and Geraci, J. E.: Photoelectric Determination of Arterial Oxygen Sat-

uration in Man, J. Lab. & Clin. Med. 34:387, 1949.

11. Wood, E. H.: A Single Scale Absolute Reading Ear Oximeter, Am. J. Physiol. 159: 597, 1949.

12. Crehan, E. L.; Kennedy, R. L. J., and Wood, E. H.: Symposium on in Vivo Photometry of Blood in Human Beings: A Study of Oxygen Saturation of Arterial Blood of Normal Newborn Infants by Means of Modified Photo-Electric Oximeter: Preliminary Report, Proc. Staff Meet. Mayo Clin. 25:392, 1950.

13. Roughton, F. J. W., and Scholander, P. F.: Microgasometric Estimation of the Blood Gases, J. Biol. Chem. 148:541, 1943.

14. Guest, G. M., and Siler, V. E.: A Centrifuge Method for Determination of the Volume of Cells in Blood, J. Lab. & Clin. Med. 19:757, 1934.

15. Mugrage, E. R., and Andresen, M. I.: Values for Red Blood Cells of Average Infants and Children, Am. J. Dis. Child. 51:775, 1936.

16. Walker, J.: Foetal Anoxia (Blair-Bell Memorial Lecture), J. Obst. & Gynaec. Brit. Emp. 61:162, 1954.

17. Turnbull, E. P. N., and Walker, J.: Haemoglobin and Red Cells in the Human Foetus: I. The Red Cells, Arch. Dis. Childhood 30:102, 1955.

18. Ingalls, T. H.; Curley, F. J., and Prindle, R. A.: Anoxia as a Cause of Fetal Death and Congenital Defects in the Mouse, Am. J. Dis. Child. 80:34, 1950.

19. Ingalls, T. H.; Curley, F. J., and Prindle, R. A.: Medical Progress: Experimental Production of Congenital Anomalies: Timing and Degree of Anoxia as Factors Causing Fetal Deaths and Congenital Anomalies in Mouse, New England J. Med. 247:758, 1952.

20. Walker, J., and Turnbull, E. P. N.: Haemoglobin and Red Cells in the Human Foetus: III. Foetal and Adult Haemoglobin, Arch. Dis. Childhood 30:111, 1955.

A Complete Program for Treatable Cerebral Palsied Children

A. W. SULLIVAN, M.D., Rochester, N. Y.

Introduciton

The term "cerebral palsy" includes the several neuromuscular disabilities which are due to a variety of lesions within the brain. The lesions may involve one or more parts of the brain in varying amounts resulting in a spectrum of types and degrees of severity of cerebral palsy. Many other handicaps are associated with this condition, including defects in vision, audition, and peripheral sensation, convulsions, orthopedic problems, retarded physical growth, emotional problems, and learning disabilities due to mental retardation, distractability, or aphasia. Because of its complexity, cerebral palsy presents a challenge in diagnosis and treatment which is best met by a multiple discipline approach in which an integrated team of consultants and therapists work in close cooperation to evaluate and develop each patient's physical and psychological resources. In this report an attempt is made to present a program for cerebral palsied children which illustrates this philosophy. This program includes a diagnostic clinic, a residential treatment center, a day treatment center, and a public school for orthopedically handicapped children which interrelate in a cooperative effort for the benefit of this group of handicapped children and their families. The aim of the program is to give service to cerebral palsied children through 12 years of age and to their parents. The program includes facilities for counseling parents, training to improve the skill of personnel, and research to discover ways of improving diagnostic and therapeutic techniques.

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From the Departments of Pediatrics and Psychiatry, Strong Memorial and Rochester Municipal Hospitals and the University of Rochester School of Medicine and Dentistry.

History of Program in Rochester, N. Y.

In 1945 the United Cerebral Palsy Association of Rochester, N. Y., was established to provide outpatient treatment facilities for children with cerebral palsy in Rochester and the vicinity. One year later this association, composed largely of parents, opened a day treatment center for cerebral palsied children.

In 1946 Dr. R. Plato Schwartz, Chairman of the Department of Orthopedics of the University of Rochester School of Medicine, initiated a program of basic researches into the synthesis and clinical use of relaxant drugs as a therapeutic tool in cerebral palsy. This study was financed in part by a grant of $292,000 by the National Foundation for Infantile Paralysis to be used for a five-year research program. In the same year the Cerebral Palsy Diagnostic Clinic, composed of an orthopedist and a neurologist, a pediatrician, a psychologist, and a social worker, was established at the Strong Memorial Hospital, the University Medical Center. Later a psychiatrist and a dental consultant were added to the clinic team.

In 1947 the Edith Hartwell Clinic was opened in Le Roy, N. Y. This residential treatment center was made possible by the gift to the University of Rochester of a large estate and sufficient money to modify it to meet the clinical needs of the therapeutic program. Cerebral palsied children under 13 years of age were accepted for intensive therapy. The Department of Health of the State of New York partially

supported its research program with state aid funds and special grants. The center was administered by The Strong Memorial Hospital.

In 1948 a close-working relationship developed between the United Cerebral Palsy Association of Rochester and the Strong Memorial Hospital Cerebral Palsy Program which included the Diagnostic Clinic and the Edith Hartwell Clinic. This relationship has given the specialty consultants a continuing contact with each child in the local program, regardless of where he received therapy.

In 1949, at the request of the Board of Education of Rochester, a committee was established under the chairmanship of Dr. R. Plato Schwartz to investigate the needs of the educable cerebral palsied children and how the public school system could participate in their education and treatment as an integral part of the local program. This survey resulted in a closer-working relationship between the cerebral palsy program and the Board of Education's School for the Orthopedically Handicapped, which sought to teach those cerebral palsied children who were educable, were 6 or more years old, and were able to care for their toilet needs. Transportation was provided from the home to the school. Education was stressed, but physical, occupational, and speech therapy was available. The school's orthopedic consultant supervised the treatment and was assisted by school consultants of other disciplines and by the Diagnostic Clinic.

Diagnostic Clinic

The Cerebral Palsy Diagnostic Clinic, established in 1946, is part of the clinic system of The Strong Memorial Hospital. It is unique in that the several regular members of the team are specialists in their fields, rather than members of the resident training program. Its personnel includes a full-time social-service worker and part-time consultants including a pediatrician, neurologist, orthopedist, psychologist, psychiatrist, and a dentist. These consultants are members of the faculty of the University of Rochester School of Medicine and Dentistry and their appointments to the Diagnostic Team was made possible by the interest and cooperation of the several departments of the school. Referrals are made to other consultative resources as necessary. Each specialist sees each child on each clinic visit. The Diagnostic Clinic meets twice monthly for 10 months during the year when two or three new patients and three to five old patients are seen.

There are many advantages in having the Cerebral Palsy Diagnostic Clinic in the teaching center: 1. In case of absence of the regular members of the team, substitutes from the hospital staff can usually be found on short notice. 2. The use of the Cerebral Palsy Diagnostic Clinic as a teaching facility for medical students and residents is implemented. 3. The availability of other specialty clinics and special laboratories facilitates the child's evaluation.

Referrals to the Diagnostic Clinic can be made only by physicians. The referring physician must have examined the child and have noted indications of cerebral palsy. This procedure is an important pre-clinic screening device which minimizes the number of non-cerebral-palsy patients, such as primary mentally retarded children, who are referred to the clinic. Children under 13 years are accepted without limitation as to sex, religion, race, economic status, or geography.

Application blanks are sent to the referring physician and the child's parents by the social worker. The diagnostic clinic's medical director approves or rejects each new application on the basis of the application data and other data obtained from hospital records and other sources.

The social worker has an hour and a half interview with the parents of new patients to obtain social case work data which is necessary for the team to understand the parents, the child, and the family setting. She discusses the diagnostic and treatment

programs with them and outlines the diagnostic clinic's procedure.[1]

A motor age test,[2] devised at the Edith Hartwell Clinic, to measure the children's motor abilities, is given, and the psychiatric and psychological evaluations of new patients are completed before the clinic meets.

When the diagnostic clinic team meets, all patients receive dental, neurological, orthopedic, and pediatric examinations. The psychiatrist and psychologist see the follow-up cases and have an opportunity to observe the new patients and their parents a second time. Chest x-rays are also obtained in accordance with the hospital policy. Other consultants and laboratory tests are obtained privately or in one of the clinics of Strong Memorial Hospital or the facilities within the community, depending upon the needs of the case.

Following the diagnostic clinic evaluation, the diagnostic staff confers regarding the diagnosis, etiology, degree of severity, and prognosis of the condition and makes recommendations for treatment, education, and the management of special problems. The conclusions arrived at in this conference are the official conclusions of the clinic.

The disposition of each case depends upon the total picture as seen by the diagnostic clinic team; the medical, psychiatric, psychological, and social evaluations are the determinants of the clinic's recommendations. Educable children may be recommended for public or private school, the outpatient treatment clinic in Rochester, or for residential treatment at the Edith Hartwell Clinic in Le Roy. Educable children from the Rochester area who are ready for regular school are recommended to the Rochester Board of Education for enrollment in special classes for orthopedically handicapped children. Some children are recommended for commitment to public institutions or day care centers for retarded children. Children who live outside the Rochester area are referred to the nearest facility for specific therapy, training, or education. Treatment and educational recommendations are sent to the clinic or school to which the child is referred. Surgery and orthopedic appliances are recommended when necessary.

Following the staff conference, a letter is sent to the parents by the social worker informing them of the clinic's diagnosis and advising them of the clinic's recommendations. They are informed that the referring physician has been sent a full report of the clinic findings and recommendations and are asked to call him for an interpretation of this report and to discuss their questions with him.

The referring physician is sent a typewritten copy of the history and the dental, pediatric, orthopedic, neurological, psychological, and psychiatric examinations as reported by the clinic team. This report is confidential and is to be used by the physician for reference in answering questions the parents may have; it is not to be given to the parents by the physician. When possible, the medical director of the clinic meets with the referring physician and discusses the clinic's findings with him. He and the social worker are always available to the referring physician or interested schools or agencies for consultation regarding the clinic's findings and recommendations.

Often the referring physician is the family's regular practitioner or pediatrician, who knows the family well and can help them to understand the problem which they must face with their child, using the data sent him by the clinic. At the request of the referring physician, the medical director of the Diagnostic Clinic meets with the parents to interpret the clinic's findings and recommendations. The clinic social worker is always available to discuss with the parents their feelings about their child's problem and his physical, intellectual, and emotional needs and to help them follow the medical recommendations.

Follow-up examinations are done periodically depending upon the needs of each child. Since the findings of the diagnostic clinic are used in deciding the therapeutic,

training, or educational programs, most of these children are seen several times over a period of several years for reevaluation and treatment recommendations. This experience gives the parents a continuous relationship with one agency where they see the same professional persons each time; thus, there is consistency in the treatment program and repeated observations of the same children over a period of years increases the clinic team's understanding of cerebral palsy and the needs of the individual children and their families.

The Edith Hartwell Clinic

The Edith Hartwell Clinic, a residential treatment center, was opened in October, 1947. It is situated 25 miles from Rochester on a large country estate and is administered by the Strong Memorial Hospital of the University of Rochester School of Medicine and Dentistry.

The Edith Hartwell Clinic has a capacity of 35 children and has an average census of 23 children. Treatable children of both sexes between 3 and 12 years of age are accepted without racial or religious limitation.

Children are usually referred to the Edith Hartwell Clinic from the diagnostic clinic. When children are referred from other cerebral palsy programs in which the diagnosis is well established, treatment recommendations have been made by competent examiners, and the distance between the hospital and home makes a regular diagnostic clinic work-up an undue hardship for the family, direct admissions may be allowed.

The Edith Hartwell Clinic is supervised by a physical therapist who is also a registered nurse; training in both fields facilitates the coordination of the efforts of the nursing service and the therapies to insure carryover of training and education among the departments.

The treatment program consists of physical, occupational, and speech therapy. Nursery school, kindergarten, and the primary school teaching is available for educable children.

The nursing department is responsible for the general care of the children as well as their care during illnesses. Feeding, bathing, toileting, preparation for bed, and sleeping are supervised by this department which employs six registered nurses and several aides to give the children continuing individualized care throughout the day and night.

The professional consultative staff, consisting of a pediatrician, a neurologist, a psychologist, an orthopedist, a psychiatrist, and a social worker are also members of the Diagnostic Clinic. The consultative medical staff makes regular visits at the Edith Hartwell Clinic to confer with the therapists, reexamine the children and make further recommendations for therapy. The dental clinic of Strong Memorial Hospital gives necessary dental care using special techniques which it developed to facilitate the dental care of cerebral palsied children. An ophthalmologist regularly evaluates each child and prescribes necessary corrective therapy.

Great emphasis is placed upon the emotional needs of the children who are temporarily away from home and need continuous contact with home. Readiness for residential treatment is evaluated prior to the child's admission. Experience has demonstrated that emotionally immature children and children under 3 years of age are inclined to have emotional reactions which seriously handicap their adjustment to the treatment program and may seriously affect their psychological development. It has also been noted that the parents' acceptance of the separation from the child is important in determining the child's acceptance of it. Thus, preparation of both the child and his parents are important in the intake process. Home visiting is allowed every week-end and parents are allowed to visit the child on week-ends when they do not take the child home. Children who live too far from the treatment center

to make regular home visits may go home for several days of visiting four or five times yearly. The home-visiting program has not presented an unusual problem of increased infection, and it has been of immeasurable value in promoting the children's emotional development and adjustment to the clinic as well as aiding in preserving the child's role in his family.

It is necessary to understand the needs of the individual child and how to meet these needs to motivate the child to participate in the treatment program so he will learn to use his muscles and skills in a meaningful way. Various types of apparatuses, including the Hartwell Carrier,[3,4] have been devised to stimulate the children's interest in the therapeutic program and to make that program as pleasant and happy an experience as possible.

Treatment progress is sometimes difficult to measure; the motor age test [1] was developed at this clinic and is used as an objective measurement of changes in psychomotor ability. This test is routinely administered to each child on admission and at trimonthly intervals while the child is in residence. It gives a numerical record of the child's development in the use of his upper and lower extremities. Colored 16 mm. motion pictures are also used to record progress; films are made of the child's activities soon after admission and at regular intervals during his residential treatment and on discharge. This pictorial record gives an accurate measure of the child's progress or lack of it. Recently a technique of using "split-frame" motion pictures has been used to record the child's longitudinal development. Motion pictures are taken of the child performing a standardized activity on one-half of the 16 mm. picture film, and after a treatment interval of up to nine months the same activity is filmed exposing the other half of the film. The result is a visual record which simultaneously compares the same performance of the child at different ages.

Parent training is also an important part of the clinic's function. The social worker of the cerebral palsy program has frequent contact with these parents particularly when there are social or other problems within the family. "Parent Days" are arranged at regular intervals when three or four pairs of parents are invited to spend the day at the Edith Hartwell Clinic. They have luncheon with the staff and spend the day visiting the various therapy departments where they observe their child's activities and have an explanation of the techniques used in their child's therapy. The psychiatrist and social worker are available to discuss with them their reaction to the separation of the child from the family and his adjustment to the clinic. Further data is accumulated which will help the staff understand some of the problems the child may be presenting. The motion picture film records of the children are shown so that each parent may have an opportunity to see the pictorial record of his child's progress during therapy as well as the progress of other children in the program.

There are also opportunities for parents to confer with the medical director of the Edith Hartwell Clinic who is one of the orthopedists of the program, and with the other consultants with whom they would like to discuss problems relative to the child's diagnosis, prognosis, treatment, and education.

Treatment Center, United Cerebral Palsy Association

A Day Treatment Clinic is administered by the United Cerebral Palsy Association of Rochester but is an integral part of the total cerebral palsy program in Rochester. The clinic is housed on a large estate located on the outskirts of the city, and is administered by a board of directors, some of whom are parents of cerebral palsied children, but most of whom are interested persons of the community with special administrative capacities. There is a medical director and an executive director who supervise the treatment and educational programs and are responsible to the board

of directors for the clinic's operation. They are assisted by the specialists of the Diagnostic Clinic who serve as treatment and education advisors.

The departments of physical therapy, occupational therapy, speech therapy, nursery school, kindergarten, and the primary grades for severely handicapped educable children give the necessary treatment and educational services.

The maintenance and office staff consists of a driver, a secretary, a half-time bookkeeper, a maintenance man, and a part-time housekeeper.

Transportation is provided for children in a limousine which has a capacity of eight children, the driver, and an attendant. Each child is taken to the clinic from his home and returned to it. Exceptions are children who have infrequent, short periods of therapy or who come from areas outside the range of the clinic's transportation service; their transportation must be arranged by the parents. Transportation is a practical problem which can impair the functioning of a day treatment center.

Recently, an adult program was established to provide recreational and occupational activities for cerebral palsied adults and to experiment with sheltered workshop techniques. A separate building was provided for this purpose. This undertaking was designed to provide a more complete service to the cerebral palsied persons in this area.

Children accepted for the Cerebral Palsy Day Treatment Center are referred through the Diagnostic Clinic. The criteria for referral are (1) a diagnosis of cerebral palsy, (2) intellectual capacity sufficient to benefit from training or education, (3) residence within a practical transportation distance from the clinic. Crippled children with treatable neuromuscular disorders are being accepted into the program more frequently as the scope of services offered to physically handicapped children is broadened.

A Parent Day Program is held once monthly. Parents are interviewed by the social worker, the executive director, and the medical director. An attempt is made to know the parents and their problems better and to share with them the clinic's observations of the child and the basis for the treatment aims. Diagnoses, complications, laboratory reports, prognosis, and the recommendations of the Diagnostic Clinic are shared with the parents at their request if they seem ready to comprehend the significance of these data. They visit each department in which the child is being treated where an attempt is made to acquaint them with the child's progress in therapy and suggestions for therapy at home are made.

In the past, parent groups have been formed in which the problems occurring in the general care of the cerebral palsy child are discussed among the parents; the medical director and social worker acted as group leaders; the physical therapists, occupational therapists, and others also participate.[1] Six evening seminars were offered twice yearly in which an attempt was made with group-discussions techniques to bring out the practical problems of child rearing, particularly of rearing the brain-damaged child. An attempt was made to recognize parental feelings and deal with them in the group and in the social-service contacts.

Recently, a parent discussion program has been initiated under the supervision of a member of the Parent Guided Observation Program of the Rochester Public School System. Interested parents of children in the day treatment program meet weekly to discuss problems in child rearing, with particular reference to the brain-damaged child. This program, using group-discussion techniques, promises to be a valuable method of parent education.

Comment

Treatment of the cerebral palsy child must consider the potentials for physical, intellectual, and emotional development of the child and the resources of his family.

Though orthopedic surgery and its allied therapies are basic in the treatment of cerebral palsy, other specialties are necessary

for an integrated effort to promote optimum development of the child's physical and psychological potentials.

Attempts must be made to integrate the efforts of the various treatment facilities and their therapy departments so that each is able to supplement the training and educational efforts of the others. Communication between the therapy staffs and the parents affords a carry-over of treatment aims from the clinics to the home through the parent education programs.

The therapeutic philosophy developed in this program is based on the premise that the cerebral palsied child needs therapy to implement the development of his potentials for growth to the end that he will improve his abilities to make use of his neuromuscular system to obtain goals important to him.[3] Physical and occupational therapy attempt to motivate the children to perform exercises which will strengthen and increase control of muscles and simultaneously teach useful activities. Passive therapy is used only when the more dynamic kinetic therapy is impractical. Braces, casts, and other appliances are used to a limited degree.

Parents of brain-damaged children need much professional help to understand the multiplicity of problems which are common among these children but are unusual among intact children. Experience has shown that many parents have great difficulty in realistically accepting their child's chronic, irreparable conditions and may need much time to work through their conflictual feelings about their handicapped child. They do so in their everyday experiences with the child, in their contacts with the therapists, consultants, social worker, psychiatrist, and in their association with other parents of cerebral palsied children.

Since cerebral palsy is often difficult to diagnose in infants, it is sometimes impossible for many months to give parents a categorical diagnosis, though they recognized the presence of a psychomotor disability. Many parents feel that the delayed diagnosis is anxiety provoking and confusing; many feel that earlier diagnosis gives them a better opportunity to adjust realistically to their child and his handicap and reduces the anxiety of wondering. In this program the parents are given the diagnosis of their child's condition as soon as it is made and, if they desire, the other complications are discussed with them so that they share our understanding of the child's capacities, limitations, and prognosis. Realistic understanding helps the parents promote better mental health for themselves, the handicapped child, and their family and to plan more realistically for the future.

Because of the complexity of the problem of diagnosing and treating cerebral palsy and in raising the cerebral palsy child, there is need for ample opportunity for parents to consult with representatives of the program.

The parent-day programs at the two treatment centers are useful in helping the parent understand his child and the handicap as well as giving them an opportunity to compare his child's difficulties with those of other cerebral palsied children of comparable age.

The parent organization is very helpful in bringing parents with this common problem together, since parent groups can help their members develop realistic attitudes toward the handicaps of their child. However, the diagnostic and treatment program should be under the direction of competent specialists in their field who work together as a team. They must guard their right to be realistic in diagnosing, prognosticating, and making recommendations. Their efforts should not be hampered by the lack of realism of well-meaning, dedicated, but untrained community groups. The professional staff should have communication with these parent groups, should understand their problems and concerns, should give them realistic guidance, but should not be directed in their professional capacities by them.

Strong Memorial Hospital, 260 Crittenden Blvd.

REFERENCES

1. Mason, M. A.: Social Services for Parents of Children with Cerebral Palsy, Cerebral Palsy Rev. 17:40, 1956.

2. Johnson, M. K.; Zuck, F. N., and Wingate, K.: Motor Age Test: Measurement of Motor Handicaps in Children with Neuromuscular Disorders Such as Cerebral Palsy, J. Bone & Joint Surg. 33-A:698, 1951.

3. Schwartz, R. P.; Zuck, F. N.; Parsons, F. H.; Wingate, K.; Lacey, T., II, and Johnson, M. K.: Motivation of Children with Multiple Functional Disabilities: Hartwell Method, J. A. M. A. 145:951, 1951.

4. Schwartz, R. P.; Zuck, F. N., and Johnson, M. K.: The Need and Resources for Stimulating Volition of Children with Cerebral Palsy; and a Report of Progress of Such Children Under In-Patient Circumstances, American Academy of Orthopedic Surgery Instructional Lecture Series, 1952, Vol. 9, p. 105.

Case Reports

Congenital Myoblastoma of the Newborn

HENRY K. SILVER, M.D., and JIMMY L. SIMON, M.D., New Haven, Conn.

Congenital myoblastoma is a rare tumor which is present at birth and usually arises from the anterior alveolar ridge in the region of the future incisor teeth. It appears as a small smooth nodule, 1 to 3 cm. in diameter, which may be sessile or polypoid and have one or more lobes. The overlying epithelium is usually intact, although in some cases ulceration of the surface has occurred. The tumor mass is nontender, firm but not hard, and increases in size very slowly. Occasionally [1] more than one distinct tumor may be found arising from the alveolar process. In 1955 Pleasants and Hinds [2] reported a myoblastoma involving the gingiva of the maxilla and pointed out that only 12 cases in the newborn infant had been reported to that time and only 3 of them had involved the mandible. Although this tumor is fully discussed in the writings of dentistry and oral surgery, very little has been written about it in the pediatric literature. The purpose of this paper is to report the fourth case of congenital myoblastoma of the newborn arising from the alveolar ridge of the lower jaw and to point out its salient features.

Report of Case

A 3375 gm. girl was born at term at the Grace-New Haven Community Hospital after an uneventful pregnancy and labor. At birth a polypoid growth was noted arising from the alveolar process of the right lower jaw (Fig. 1). The mass consisted of four separate lobes, the largest being 1.5×0.5 cm. and the smallest, 0.3×0.3 cm. The tumor was rubbery in consistency, nontender, not inflamed, and covered with epithelium. No other anomalies were noted, nor were any revealed in the family history. One older sibling was living and well. The infant was able to nurse at the breast without difficulty. Roentgenograms of the mandible revealed no evidence of bone or tooth elements in the mass.

Fig. 1.—Patient with congenital myoblastoma of the newborn, aged 3 days.

On the fourth day of life the tumor was excised by Dr. Donald P. Shedd. Histologically the entire tissue mass consisted of large polygonal cells with very small nuclei. The cell membranes were distinct, and the voluminous cytoplasm was quite pale on staining and contained small acidophilic granules. The nuclei were round and stained evenly. Interspersed in the tumor tissue were small collections of round cells of the histiocytic type (Fig. 2). Pathologic diagnosis was granular-cell myoblastoma.

Postoperatively the infant continued to nurse well at the breast and left the hospital with her mother on the fifth day of life.

Comment

Although Abrikossoff [3] was the first to differentiate the myoblastoma as a tumor

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From the Department of Pediatrics, Yale University School of Medicine. Dr. Silver is now Professor of Pediatrics at the University of Colorado School of Medicine.

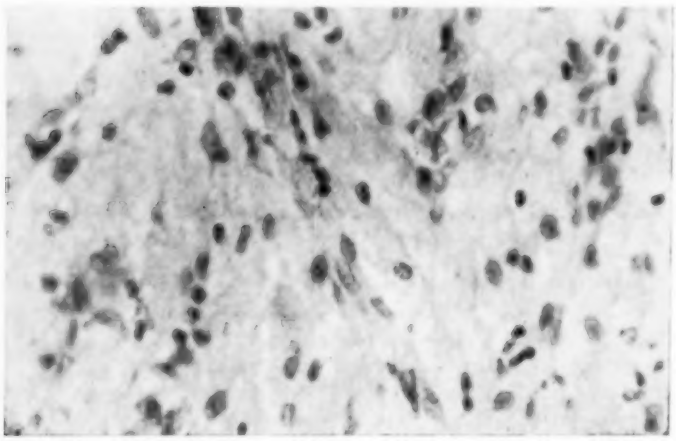

Fig. 2.—Photomicrograph of congenital myoblastoma of the newborn.

entity, in 1926, it had been described many years previously.[4-7] The tumor affects many sites, the commonest being the oral cavity (tongue, lips, and jaws). However, myoblastomas have also been found in the larynx, esophagus, orbit, external auditory canal, breasts, skin and muscles of the extremities. Those arising from the alveolar ridges were almost always present in the neonatal period.

Histologically, the tumor is characterized by large polyhedral cells 20-60μ in diameter with small distinct nuclei and a coarse neutrophilic granular cytoplasm. Because of the foamy appearance, it may be confused with a xanthomatous tumor. From the reported cases in the literature it appears that the myoblastomas of the newborn are benign lesions, although granular-cell myoblastomas in older persons may be either benign or malignant.[8] Treatment consists of local excision, which should effect complete cure. Recurrences of the growth are not to be expected providing complete removal has been accomplished.

There is no uniformity of opinion as to the nature and origin of this tumor. Custer and Fust[9] believe that they arise from neural elements and are "granular cell neurofibromas." Karsner,[10] Abrikossoff,[11] and others feel that their origin is from striated muscle elements, and this is in keeping with the most widely accepted theory, that they represent a dysontogenesis of embryonal skeletal muscle. However, the exact classification of this tumor is still open to question.

The myoblastoma of the newborn is clinically indistinguishable from the so-called "congenital epulis of the newborn," which also commonly involves the gingiva of the alveolar ridge of the newborn infant. Many authors[11-15] consider both tumors to be different forms of the same underlying condition, but others[4] believe that the congenital epulis arises as a malformation of the dental blastema and is a distinct entity from the myoblastomas.

The myoblastoma must also be differentiated from the acquired epulis which is not a true neoplasm but represents an inflammatory hyperplasia of the gingival mucosa.

Summary

The fourth case of myoblastoma of the newborn arising from the alveolar ridge of the lower jaw is reported, and its salient features are described.

Drs. Harold S. Fleming and Donald P. Shedd provided helpful suggestions for this report.

4200 Ninth Avenue, Denver (H. K. S.)

REFERENCES

1. Crane, A. R., and Tremblay, R. G.: Myoblastoma, (Granular Cell Myoblastoma or Myoblastic Myoma), Am. J. Path. 21:357, 1945.

2. Pleasants, J. E., and Hinds, E. C.: Granular Cell Myoblastoma, Oral Surg. 8:698, 1955.

3. Abrikossoff, A.: Über Myoma ausgehend von der quergestreiften willkürlichen Muskulatur, Arch. path. Anat. 260:215, 1926.

4. Weber, C. O.: Anatomische Untersuchung einer hypertrophischen Zunge nebst Bemerkungen über die Neubildung quergestreifter Muskelfasern, Arch. path. Anat. 7:115, 1854.

5. Heurtaux, J.: Tumeur de la langue (dégénérescence granulo-protéique des fibres musculaires), J. méd. l'ouest, Nantes 15:305, 1881.

6. Pendl, F.: Über ein congenitales Rhabdomyom der Zunge, Ztschr. Heilk. 18:457-468, 1897.

7. Moschcowitz, E.: Xanthoma (Xanthelasoma) of the Tongue, Proc. New York Path. Soc. 22:135, 1922.

8. Ackerman, L.: Surgical Pathology, St. Louis, The C. V. Mosby Company, 1953.

9. Custer, R. P., and Fust, J. A.: Congenital Epulis, Am. J. Clin. Path. 22:1044, 1952.

10. Karsner, H. T.: Human Pathology, Ed. 7, Philadelphia, J. B. Lippincott Company, 1949.

11. Abrikossoff, A.: Weitere Untersuchungen über Myoblastenmyome, Arch. path. Anat. 280: 723, 1931.

12. Kühne, W.: Beitrag zur Histogenese der Epulis congenita, Beitr. Anat., Physiol., Path. u. Therap. Ohres. 31:94, 1935.

13. Kerr, D. A.: Myoblastic myoma, Oral Surg. 2:41, 1949.

14. Sternberg, C., in discussion of Klinge, F.: Ueber die sogenannten unreifen, nicht quergestreiften Myoblastenmyome, Verhandl. deutsch. path. Gesellsch, 23:376, 1928.

15. Bernier, J. L., and Thompson, H. C.: Myoblastoma, J. Dent. Res. 25:253, 1946.

Abstracts from Current Literature

A. M. A. Archives of Internal Medicine, Chicago

98:541-682 (Nov.) 1956

* Newer Agents in the Treatment of Leukemia. Joseph H. Burchenal and Irwin H. Krakoff.—p. 567.
Infectious Diseases. Annual Review of Signicant Publications. Hobart A. Reimann.—p. 639.

97:661-820 (June) 1956

* Sensitivity of Various Clinically Important Bacteria to Seven Antibiotics. Lowell A. Rantz and Helen H. Rantz.—p. 694.
* Evaluation of CB 1348 in Hodgkin's Disease and Allied Disorders. Bertha A. Bouroncle, Charles A. Doan, Bruce K. Wiseman, and Walter J. Frajola.—p. 703.
Pseudohemophilia Type B. Karl Singer and Bracha Ramot.—p. 715.
Canicola Fever with Meningitis. Samuel Dvoskin and Edward W. Hook.—p. 793.
Encephalopathy Due to Influenza Vaccine. Willard R. Warren.—p. 803.

98:1-128 (July) 1956

* Clinical and Laboratory Studies of Novobiocin, a New Antibiotic. William M. M. Kirby, Dean G. Hudson, and Ward D. Noyes.—p. 1.
Respiratory Manifestations of Chicken Pox. Louis Weinstein and Richard H. Meade.—p. 91.

98:129-256 (Aug.) 1956

* Rheumatic Fever. Gene H. Stollerman.—p. 211

98:257-388 (Sept.) 1956

* A Clinical and Bacteriologic Evaluation of Novobiocin in Seventy-Five Patients. Joyce Z. Pearson, Alvin Somberg, Ira Rosenthal, Mark H. Lepper, George Gee Jackson, and Harry F. Dowling.—p. 273.
Human Infection Caused by the Mimeae Organisms. Albert Minzter.—p. 352.
* A Family Epidemic of Psittacosis with Occurrence of a Fatal Case. Robert L. Prouty and William S. Jordan Jr.—p. 365.

Newer Agents in the Treatment of Leukemia.—In this article the authors summarize the status of the newer agents which are available for the treatment of leukemia. In the treatment of acute leukemia the antimetabolites appear to be the main reliance of the therapist and the backbone of long-range therapy. The authors point out that these antimetabolites require three to eight weeks to exert the beneficial effect.

The steroids, which work much faster but which produce much shorter remissions, should be saved for emergencies in which the rapidity of action is essential. Of the folic acid antagonists, the authors favor the use of Amethopterin (Methotrexate).

The authors also describe the use of several new chemotherapeutic agents which appear to be active in chronic leukemias, but they point out that enough work has not been done with these new agents to determine how they will compare with the more conventional x-ray therapy and P^{32}.

Sensitivity of Various Clinically Important Bacteria to Seven Antibiotics.—The authors describe a relatively simple screening procedure for estimating the sensitivity of bacteria to antibiotics. This method consists of exposing organisms to a single arbitrarily selected concentration of the antimicrobial agent contained in a blood agar plate. Antibiotics which inhibited growth are considered as being effective agents for the given organism, and if growth was found on the plate the organisms are considered as resistant. The plates were read at 24 hours. The clinical correlations were good. The body of the report consists of a description of their study of the antibiotic sensitivity of 1698 strains of bacteria which were isolated between May, 1954, and August, 1955. Their conclusions are much the same as those of other workers in this field. Micrococcus pyogenes var. aureus, Escherichia coli, paracolon bacilli, and Proteus have become more frequently resistant to one or more antibiotics during the past several years, while hemolytic and nonhemolytic streptococci have continued to be sensitive to many antibiotics. These observations emphasize the importance of in vitro testing of isolated bacteria in planning the management of patients who have received previous antibiotic therapy. This is particularly true of those patients with infections of the urinary tract.

Evaluation of CB 1348 in Hodgkin's Disease and Allied Disorders.—There has been a continued search for an effective chemical dirivative of nitrogen mustard which may be taken orally and which will not have the side-effects of bone-marrow depression, nausea, vomiting, and malaise. The authors report their studies on 42 patients with Hodgkin's disease and other allied disorders treated with *p*-bis(2-chloroethyl) aminophenylbutyric acid (CB 1348). This new drug appears to be safer than TEM, because it does not have the erratic and often unpredictable effect that characterizes TEM. It may be taken orally and is usually free of side-effects and does not depress the peripheral blood and bone marrow as much as nitrogen mustard. Excellent remissions were obtained in six patients with Hodgkin's disease, one patient with reticulum-cell sarcoma, and one patient with monocytic leukemia. Marked improvement was obtained in nine patients with Hodgkin's disease. Patients with chronic lymphatic leukemia, lymphosarcoma, acute lymphatic leukemia, mycosis fungoides, and multiple myeloma were not helped. It is concluded that this drug is of value in the treatment of selected patients with Hodgkin's disease as a supplement to x-ray therapy.

Clinical and Laboratory Studies of Novobiocin, a New Antibiotic.—Novobiocin is a new antibiotic which appears to be effective against the commonly encountered Gram-positive bacteria and also against certain Gram-negative bacteria. Of particular importance is the fact that staphylococci resistant to other antibiotics are highly susceptible to novobiocin. The authors report their experience with this new drug in 75 patients. Staphylococci were remarkably sensitive in vitro, and there was no cross-resistance with other antibiotics. Clinical results were in general favorable, and they appeared comparable to those obtained with erythromycin. For staphylococcal infections where prompt healing did not occur, the infecting organisms rapidly became resistant to novobiocin. For this reason it was recommended that this new antibiotic be used exclusively for the treatment of infections caused by antibiotic-resistant staphylocci and, wherever possible, another antibiotic should be administered simultaneously. All patients received 2.0 gm. daily in divided doses, and there was remarkable freedom from side-effects.

Rheumatic Fever.—This article is a short but comprehensive review of the current trends in the treatment of rheumatic fever. As this article is strictly a review article, it does not lend itself to abstracting. Although this article contains nothing new, it does offer a short review of the current ideas in the management of these patients. For those interested in this topic, the original article should be read in its entirety.

A Clinical and Bacteriologic Evaluation of Novobiocin in Seventy-Five Patients.—The authors give a detailed report of their experience with the new antibiotic, novobiocin, in 75 patients with a variety of bacteriologic infections. Their results were in general agreement with other groups who have studied this new drug. Prior to clinical trial, novobiocin showed great promise because of the extreme sensitivity which most strains of Staphylococcus showed in in vitro studies. The clinical and bacteriologic response of patients with staphylococcal infections treated with this new drug in general corroborates the laboratory evidence for the effectiveness of the agent in suppressing the growth of staphylococci. However, there were a significant number of patients in which the clinical response was poor and another group in which the staphylococci had persisted in specimens that were cultured for bacteria near the conclusion of the treatment. After treatment, these strains showed remarkable resistance to novobiocin.

This drug frequently failed to eradicate offending organisms from infections caused by other Gram-positive cocci, namely, Diplococcus pneumoniae, Streptococcus pyogenes, and enterococcus.

In contrast to other clinical studies with this drug, the authors found rather high frequency of drug reaction, i. e., 18.7%. Skin eruptions were the commonest, but also observed was a significant leukopenia. Because of the development of resistance to novobiocin by the strains of Staphylococcus, it is recommended that other antibiotics that may possibly suppress the emergence of such strains should always be used concomitantly when the treatment is expected to be prolonged.

A Family Epidemic of Psittacosis with Occurrence of a Fatal Case.—The authors report four cases of Psittacosis which occurred in a family of 12 persons exposed to two apparently healthy parakeets. There was one death among this family and the three other members afflicted had manifestations which ranged from severe illness to inapparent infections.

Psittacosis viruses were recovered from the lung of the fatal case and also from a parakeet obtained from the store that sold the infected birds to this family.

The authors point out that clinical evidence of infection in children is unusual, and, in general, infections in younger persons result in inapparent disease. In this family of 10 children, the 2 oldest, ages 18 and 16, became ill, but only one had laboratory evidence of infection. One child, aged 10, developed a diagnostic antibody titer, although he had no symptoms of the disease. The increasing number of human cases of psittacosis calls for a reconsideration of control measures, including education of the public and legislation.

The authors point out that the most dangerous bird source is still the parakeet which is introduced into the home as a pet. The medical profession should be aware of the increasing incidence of psittacosis and of the wide manifestations which this disease may take.

American Heart Journal, St. Louis

52, No. 5 (Nov.) 1956

* The Effect of Background Noise on Cardiac Auscultation. Dale Groom, S. C. Charleston, with the Technical Assistance of Oren Herring, Wofford Francis, and Gibson Shealy.—p. 781.

The Effect of Background Noise on Cardiac Auscultation.—All clinicians, and perhaps pediatricians in particular, are aware of the masking effect that background noise has on the audibility of cardiac murmurs. In this article the author presents, in quantitative form, the degree to which background noise in the clinical environment actually impairs one's ability to hear heart murmurs through the stethoscope.

To carry out the study a relatively sound-proof room was constructed in which ambient room noise was reduced to the 35 db. level, based on a 0 db. level at the threshold of human hearing. By comparison, measurements taken with a sound level meter in various parts of the hospital indicated that the ambient room noise in areas where patients were usually examined was in the range of 60-70 db.

Forty physicians, including members of the faculty and house staff of the hospital, served as subjects in the experiment. In the sound-proof room a tape-recorded diastolic murmur was reproduced on a sound channel in such a way that auscultation of the murmur could be carried out with a stethoscope through a medium approximating the acoustical properties of flesh. A second sound channel was used to introduce background noise raising the sound pressure to which the subject was exposed from 35 to 65 db. The threshold at which the murmur was first perceptible was measured for the 40 subjects first at a background noise level of 35 db. and then at 65 db. Without exception all the subjects required an increase in intensity of the murmur for it to be perceived when the background noise was raised—the average increase being 11.8 db., which represents an increase in intensity of the murmur of more than 12 times. Professional experience did not improve the subjects ability to detect the murmur at the higher background noise levels.

The article confirms the clinical observation that high levels of background noise significantly interfere with accurate auscultation of cardiac murmurs and stresses the point that a really quiet examining room (and patient) are necessary for accurate auscultatory diagnosis.

The American Journal of Medicine, New York

21, No. 2 (Aug.) 1956

The Case for Viral Diarrheal Disease. A. R. Higgins.—p. 157.

* Clinical and Laboratory Studies in Patients with Respiratory Disease Caused by Adenoviruses (RI-APC-ARD Agents). H. E. Dascomb and M. R. Hilleman.—p. 161.

Coxsackie Viruses and "Virus-like" Diseases of the Adult: A Three-Year Study in a Contagious Disease Hospital. Edwin D. Kilbourne and Martin Goldfield.—p. 175.

Outbreak of Unusual Form of Pneumonia at Camp Gruber, Oklahoma, in 1944: Follow-up Studies Implicating Histoplasma Capsulatum as the Etiologic Agent. A. E. Feller, Michael L. Furcolow, Howard W. Larsh, Alexander D. Langmuir, and John H. Dingle.—p. 184.

Ox Cell Hemolysins in Infectious Mononucleosis and in Other Diseases. E. Taylor Peterson, R. L. Walford, William G. Figueroa, and Roberta Chisholm.—p. 193.

Constitutional Non-Hemolytic Jaundice with "Lipochrome" Hepatosis (Dubin-Sprinz Disease). Norman L. Brown and Theodor K. Shnitka.—p. 292.

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Insulin I-131 Metabolism in Man: Plasma-Binding, Distribution and Degradation. George W. Welsh, III, Elaine D. Henley, Robert H. Williams, and Robert W. Cox.—p. 324.

Humoral Insulin Antagonism Associated with Diabetic Acidosis. James B. Field and DeWitt Stetten Jr.—p. 339.
* Stable and Brittle Diabetes. John G. Alivisatos and E. Perry McCullagh.—p. 344.
Observations of Human Adrenal Cortical Deficiency, with Special Reference to Replacement Therapy with Cortisone. A. Gorman Hills, Harold A. Zintel, and David W. Parsons.—p. 358.
The Clinical Significance of the Analysis of Serum Protein Distribution by Filter Paper Electrophoresis. William P. Jencks, Elizabeth R. B. Smith, and E. L. Durrum.—p. 387.
Cystic Fibrosis of the Pancreas. Paul A. di Sant'Agnese.—p. 406.
Multiple Pulmonary Arteriovenous Fistulas in Juvenile Cirrhosis. Robert Rydell and F. W. Hoffbauer.—p. 450.
Superior Vena Cava Draining into Left Atrium. Another Cause for Left Ventricular Hypertrophy with Cyanotic Congenital Heart Disease. Herman Tuchman, John F. Brown, John H. Huston, Arvin B. Weinstein, George G. Rowe, and Charles W. Crumpton.—p. 481.

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* Penicillamine, a New Oral Therapy for Wilson's Disease. J. M. Walshe.—p. 487.
Renal Vein Thrombosis and the Nephrotic Syndrome. Victor E. Pollak, Robert M. Kark, Conrad L. Pirani, Harold A. Shafter, and Robert C. Muehrcke.—p. 496.
Exacerbation of Lupus Erythematosus Following Splenectomy in "Idiopathic" Thrombocytopenic Purpura and Autoimmune Hemolytic Anemia. William Dameshek and W. Harriton Reeves.—p. 560.
Observations on Hepatic and Renal Dysfunction in Trichinosis: Anatomic Changes in These Organs Occurring in Cases of Trichinosis. Joseph M. Guattery, John Milne, and Reginald K. House.—p. 567.
Hyperparathyroidism. Morton D. Bogdonoff, Alexander H. Woods, J. Earle White, and Frank L. Engel.—p. 583.
Idiopathic Hypoparathyroidism and Addison's Disease. Martin Perlmutter, Rose Ruth Ellison, Luigia Norsa, and Abraham R. Kantrowitz.—p. 634.
Pseudohypoparathyroidism. C. E. Butterworth Jr., L. C. Hamilton, and Norman Zheutlin.—p. 644.
Dyschondroplasia with Soft Tissue Calcification and Ossification, and Normal Parathyroid Function ("Pseudo-Pseudohypoparathyroidism"). William F. McNeely, Lawrence G. Raisz, and Marjorie LeMay.—p. 649.

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The Cytotoxic Action of Carcinolytic Agents in Tissue Culture. Harry Eagle and George E. Foley.—p. 739.
Hypercalcemia in Malignant Disease Without Evidence of Bone Destruction. Calvin H. Plimpton and Alfred Gellhorn.—p. 750.
Extreme Obesity Associated with Alveolar Hypoventilation—A Pickwickian Syndrome. C. Sidney Burwell, Eugene D. Robin, Robert D. Whaley, and Albert G. Bickelmann.—p. 811.
A Peculiar Type of Cardiopulmonary Failure Associated with Obesity. Douglas Carroll.—p. 819.

Clinical and Laboratory Studies in Patients with Respiratory Disease Caused by Adenoviruses (RI-APC-ARD Agents).—Dascomb and Hilleman report their clinical observation on 45 hospitalized Army recruits in whom evidence of infection by type 7 Respiratory Infection virus was provided by fourfold or greater rise in complement-fixation titer, by significant rises in neutralization titer in the 12 serums so tested, and by recovery of the virus on tissue culture in 11 of the 45. Hemagglutination tests for Inflenza virus and cold and streptococcic MG agglutinations were negative. Although β-hemolytic Streptococcus was occasionally isolated, in only one patient was there a rise in A. S. O. titer.

This respiratory infection had a basic syndrome of fever, pharyngitis, and debilitating cough associated with one or more of the following: a granular conjunctivitis, serous or mucopurulent rhinitis, catarrhal otitis media, laryngitis, tracheobronchitis, and pneumonitis. In two-thirds the onset was gradual with fever rising to 102 F (range 100 F to 104 F). Myalgia, malaise, and headache were frequent. The pharynx initially appeared bright red and edematous. After two days patches of posterior pharyngeal lymphoid tissue became prominent and, in 50%, areas of white exudate appeared on the pharyngeal and tonsillar lymphoid tissue, often accompanied by cervical adenopathy. The white blood count ranged from 7000 to 33,000, with a mean of 12,200. Typically the duration of hospitalization was about 9 days, with a range of 4 to 33 days.

It is apparent the viruses of the Respiratory Infection family have been responsible for a wide variety of illnesses including the undifferentiated acute respiratory disease (A. R. D.), pharyngoconjunctival fever, nonstreptococcic exudative pharyngitis, and primary atypical pneumonia without cold or streptococcic M. G. agglutination. The frequency of this infection is seen from the fact that the 45 cases here reported came from 50 randomly selected admissions during an epidemic of respiratory illnesses.

Stable and Brittle Diabetes.—The arguments concerning the sequelae of diabetes managed with a strict diet as compared with a "free" regimen depend in part upon definitions of control. Alivisatos and McCullagh divided their 172 diabetics over 24 years of age into stable and brittle groups, the brittle (insulin sensitive) diabetics being those with a high

percentage of blood sugars taken at random throughout the day of either less than 120 mg. or more than 200 mg., with a high percentage (>15%) of days on which the spread of results of random blood sugars was greater than 100 mg., with frequent (>5%) blood sugars below 60 mg. per 100 cc., and with consistent and frequent appearance of ketonuria. Divided on this basis the ratio of women to men was 1.69:1 for brittle diabetics and 1.19:1 for stable diabetics. The brittle diabetics were found to have much more frequent attacks of hypoglycemia and 86% were sensitive to physical work. In contrast, in 87% of the stable diabetics hypoglycemia related to work had never occurred. Of the stable diabetics 23% were 20 lb. or more above their ideal weight, whereas 77% had been similarly overweight when at their maximum. Only 3% of the brittle diabetics were 20 lb. overweight when examined and only 20% had been when at their maximum. Insulin lipodystrophy occurred in 29% of the brittle diabetics and none of the stable group.

The incidence of degenerative complications was higher in the patients with stable diabetes. In those with diabetes of over 10 years' duration, 2% of the brittle group and 20% of the stable group had diabetic retinopathy of grade III or IV. Similarly, 70% of the brittle group were without evidence of arteriosclerosis or hypertension while 69% of the stable had evidence of such complications. Within the stable group those patients who had more frequent elevated blood sugars had a significantly higher incidence of late degenerative complications than did those with "good control."

Penicillamine, a New Oral Therapy for Wilson's Disease.—Patients with hepatolenticular degeneration have been demonstrated to have high levels of tissue copper, low serum copper, and high urinary copper. It has been suggested that the primary metabolic defect is an inability to handle copper due to a deficiency in ceruloplasmin. To increase copper excretion, BAL has been given to patients with Wilson's disease; but to be effective in ameliorating symptoms the drug must be given early in the disease and for long periods of time. Because BAL has been variable in its results and because toxicity has been frequent, other mono- and dithiols were tested for their copper-chelating effect. Of those tested by Walshe, only penicillamine (or β,β-dimethyl cysteine, a degradation product of penicillin) was found to have a significant effect. Given in doses of 300 mg. P. O. t. i. d., this drug caused a twentyfold increase in urinary copper excretion in six patients with Wilson's disease. In all but one patient the excretion was greater after penicillamine given by mouth than after BAL given intramuscularly. The total amounts of copper excreted daily during penicillamine therapy was three to four times the dietary copper intake. This limited study suggests that penicillamine may be effective in Wilson's disease. However, this report does not describe the clinical results of the therapy. Although no toxicity was noted, the theoretical possibility of a block in the metabolism of cysteine exists.

American Journal of Pathology, Ann Arbor, Mich.

32, No. 5 (Sept.-Oct.) 1956

Multiple Small Arteriovenous Fistulae of the Lungs. Milton R. Hales.—p. 927.

Varicella: Report of Two Fatal Cases with Necropsy, Virus Isolation, and Serologic Studies. William J. Cheatham, Thomas H. Weller, T. F. Dolan Jr., and John C. Dower.—p. 1015.

The Endocrine Significance of Hypophyseal Tumors in Man. Agnes B. Russfield, Leopold Reiner, and Hanna Klaus.—p. 1055.

American Review of Tuberculosis and Pulmonary Diseases, New York

74:655-819 (Nov.) 1956

Differential Characteristics in Vitro and in Vivo of Several Substrains of BCG: I. Multiplication and Survival in Vitro. René J. Dubos and Cynthia H. Pierce.—p. 655.

Differential Characteristics in Vitro and in Vivo of Several Substrains of BCG: II. Morphologic Characteristics in Vitro and in Vivo, Cynthia H. Pierce and René J. Dubos.—p. 667.

Differential Characteristics in Vitro and in Vivo of Several Substrains of BCG: III. Multiplication and Survival in Vivo. Cynthia H. Pierce, René J. Dubos, and Werner B. Schaefer.—p. 683.

Differential Characteristics in Vitro and in Vivo of Several Substrains of BCG: IV. Immunizing Effectiveness. René J. Dubos and Cynthia H. Pierce.—p. 699.

The Intracellular Activation of Pyrazinamide and Nicotinamide. G. B. Mackaness.—p. 718.

Measurement of Functional Residual Capacity: A Comparison of Two Closed-Circuit Helium-Dilution Methods. Robert S. Weiner and Philip Cooper.—p. 729.

The Physiologic Disposition of Cycloserine in the Human Subject. Gaylord M. Conzelman Jr.—p. 739.

Serologic Investigations of Mycobacterial Antigens: III. Direct Detection of Homologous Antibodies by BCG Extract Antigens in Serums of Rabbits Injected with BCG and Challenged with Mycobacterium Bovis. John R. Thurston and Melvin Rheins.—p. 756.
Serologic Investigations of Mycobacterial Antigens: IV. Further Serologic Characterization of BCG Extract Antigens. Melvin Rheins and John R. Thurston.—p. 764.
* Steatorrhea and Probable Tuberculosis with Acquired Hypogammaglobulinemia. H. H. Zinneman and Wendell H. Hall.—p. 773.
Allergy to Isoniazid: Successful Immunization in Two Cases. Halla Brown, Gerald Goldstein, and George Chapman.—p. 783.
Antimicrobially Active Concentrations of Salizid® and Isoniazid in the Blood. W. Mandel et al.—p. 796.
On the Physiologic Disposition of Cycloserine in Experimental Animals. G. M. Conzelman Jr. and R. K. Jones.—p. 802.

74:820-988 (Dec.) 1956

Pneumoencephalography in Tuberculous Meningitis. Eldon L. Foltz and Thomas F. Sheehy Jr.—p. 835.
Differential Diagnosis Between Beryllium Poisoning and Sarcoidosis. Harrier L. Hardy.—p. 885.
U. S. Veterans Administration—Armed Forces Cooperative Studies of Tuberculosis: V. Antimicrobial Therapy in the Treatment of Primary Tuberculous Pleurisy with Effusion: Its Effect upon the Incidence of Subsequent Tuberculous Relapse. Abraham Falk and William W. Stead.—p. 897.
Studies on Prevention of Experimental Tuberculosis with Isoniazid: II. Effects of Different Dosage Regimens. Carroll E. Palmer, Shirley H. Ferebee, and Louise Hopwood.—p. 917.
* Primary Mediastinal Cysts and Neoplasms in Infants and Children. F. Henry Ellis Jr. and James W. DuShane.—p. 940.
A Simple Technique for the Differentiation of Tubercle Bacilli and Saprophytic Mycobacteria. J. F. Coster and A. Manten.—p. 958.
Toxicity and Pharmacology of Cycloserine. Harry J. Robinson et al.—p. 972.

Steatorrhea and Probable Tuberculosis with Acquired Hypogammaglobulinemia.—Chronic steatorrhea, which appeared to be the result of tuberculous mesenteric lymphadenitis, preceded by four years the appearance of acquired hypogammaglobulinemia in a young man. The almost complete absence of gamma globulin from the patient's serum proteins did not abolish delayed skin sensitivity to tuberculin, contrary to some earlier opinions which maintained that positive Mantoux reactions could not be expected in hypogammaglobulinemia. While patients with hypogammaglobulinemia are an easy prey to infections with pneumococci, meningococci, and streptococci, this patient recovered promptly from tuberculous infection in spite of hypogammaglobulinemia.

It is suggested that acquired hypogammaglobulinemia often occurs as a sequal to a pathologic process involving the lymphatic system.

Steatorrhea is among the most frequent signs of the syndrome of acquired hypogammaglobulinemia and has been demonstrated in 6, and probably 7, of a total of 32 patients with this syndrome.

Primary Mediastinal Cysts and Neoplasms in Infants and Children.—The authors have reported on 58 children with mediastinal cysts or neoplasms of the mediastinum.

Symptoms were present in 35 of the 58 patients. The commonest symptoms were those referable to the respiratory tract, namely, cough, dyspnea, and pain. Symptoms were more commonly associated with teratomatous tumors, enterogenous anomalies and malignant lesions of all varieties than with any other type of mediastinal lesion. Patients with benign neurogenic tumors and those with vascular tumors were notably asymptomatic.

Neurogenic tumors and teratomatous tumors together represented more than 60% of all the cases. Vascular lesions and cystic hygromas were observed to occur more frequently in this group of infants and children than in adults. There were no instances of mediastinal goiter, thymoma, or coelomic cyst, in contrast to the findings in adults.

A malignant tumor was present in 14 (24%) of the 58 patients. Comprising these 14 were the following: neuroblastma, 4; neurofibrosarsoma, 1; teratocarcinoma, 3; angiosarcoma, 2, and Grade 4 malignant neoplasm (unclassified), 4.

Annals of Internal Medicine, Lancaster, Pa.

44, No. 6 (June) 1956

Viral Hepatitis: Descriptive Epidemiology Based on Morbidity and Mortality Statistics. Ida L. Sherman and Heinz F. Eichenwald.—p. 1049.
* Clinical and Physiologic Aspects of Closure of Atrial Septal Defects by the Atrioseptopexy Technic. Janet Dickens, Harry Goldberg, and Daniel F. Downing.—p. 1088.
Gaucher's Disease and Pregnancy: Two Case Reports, Including Observations on the Effects of Adrenal Steroids. Barry Decker and C. A. McWhorter.—p. 1219.
Editorial—The Sensitized Sheep Cell Agglutination Reaction in Rheumatoid Arthritis.—p. 1270.

Clinical and Physiologic Aspects of Closure of Atrial Septal Defects by the Atrioseptopexy Technic.—Fifty symptomatic patients (thirty-seven with ostium secundum and thirteen with ostium primum), 5 to 51 years of age, were operated upon. Four had mitral stenosis, three mitral insufficiency, three tricuspid insufficiency, and ten partial anomalous pulmonary venous return as well as the septal defect. Dyspnea and decreased exercise tolerance were the most frequent symptoms; congestive failure occurred in 22 (44%). The important physical findings were left sternal border systolic murmur (90% of patients), left sternal border early diastolic murmur (22%), apical mid-diastolic or presystolic murmurs (22%), and accentuated pulmonic second sound (90%). Two plus or greater enlargement by x-ray of the heart as a whole occurred in 79%, of the pulmonary artery segment in 90%, and of the pulmonary vascular markings in 81%. Electrocardiograms showed right ventricular hypertrophy and strain in 57%, complete bundle branch block in 22%, incomplete bundle branch block in 15%, first degree atrioventricular block in 15%, arrhythmias in 15%, and no abnormality in 11%. Pure left-to-right shunts of more than 1 liter per minute were found by heart catheterization in 86%, while 7% had bidirectional shunts and another 7% had little flow in either direction. Some degree of pulmonary hypertension was present in 73% and arterial desaturation in 44%. Definite correlation between pulmonary artery pressure or flow and heart size or right ventricular hypertrophy and strain in the electrocardiogram could not be demonstrated.

Postoperative mortality (eight patients with ostium primum and five with ostium secundum) and morbidity were associated with cardiac arrest, arrhythmias, congestive failure, incomplete closure of the defect, hypotension, obstruction of the orifice of the vena cava, pulmonary infarcts, and cerebral emboli. Twenty-one patients (42%) became asymptomatic after surgery and six (12%) were improved but still complained of some dyspnea and fatigue on exertion, while two (4%) were unimproved. Eight patients were not followed. Postoperative cardiac catheterization in 24 patients showed that the left-to-right shunt was eliminated in 22; of 12 cases with preoperative pulmonary hypertension, the pulmonary artery pressure fell to normal in 8, was significantly decreased in one and remained elevated in 3.

Blood, New York

11, No. 9 (Sept.) 1956

* Hemorrhagic Disease with Circulating Inhibitors of Blood Clotting: Anti-AHF and Anti-PTC in Eight Cases. J. H. Lewis, J. H. Ferguson, and T. Arends.—p. 846.

Studies on the Biosynthesis of Heme in Vitro by Avian Erythrocytes. A Goldberg, H. Ashenbrucker, G. E. Cartwright, and M. M. Wintrobe.—p. 821.

Normal Bone Marrow Total Cell and Differential Values by Quantitative Analysis of Particle Smears. S. Sandkuhler and E. Gross.—p. 856.

11, No. 9 (Oct.) 1956

Two "Fast" Hemoglobin Components in Liberian Blood Samples. Abner R. Robinson, Wolf W. Zuelzer, James V. Neel, Frank B. Livingstone, and Max J. Miller.—p. 902.

On the Prevalence of Hemoglobin D in the American Negro. Amoz I. Chernoff.—p. 907.

* The Effects of Varying Concentrations of Human Platelets and Their Stored Derivatives on the Recalcification Time of Plasma. Edmund Klein, Sidney Farber, Gustave Freeman, and Rosemary Fiorentino.—p. 910.

Reticulocytopenia in Autoimmune Hemolytic Anemia. William H. Crosby and Henry Rappaport.—p. 929.

Relative Effectiveness of Phenylhydrazine Treatment and Hemorrhage in the Production of an Erythropoietic Factor. Elly M. Jacobsen, A. K. Davis, and Edward L. Alpen.—p. 937.

Hemorrhagic Disease with Circulating Inhibitors of Blood Clotting: Anti-AHF and Anti-PTC in Eight Cases.—Eight patients with bleeding tendency were found to have a circulating inhibitor of clotting. The inhibitor was identified as Anti-AHF in five patients with AHF deficiency (hemophilics) and Anti-PTC in two PTC-deficient patients. Anti-AHF and Anti-PTC were demonstrated by incubating the patient's plasma with normal plasma and then demonstrating the fall in titer of the AHF or PTC content of the mixture. In contrast, when ordinary hemophilic or PTC-deficient plasma was incubated with normal plasma no decrease in AHF or PTC content of the normal plasma was demonstrable.

In one "idiopathic case" there was no lack of plasma factors AHF or PTC, but there were found very powerful inhibitors to both, anti-AHF predominating.

Factors which may have induced the formation of these inhibitors included repeated transfusions of blood and plasma in all and a previous pregnancy in the "idiopathic" case.

The Effects of Varying Concentrations of Human Platelets and Their Stored Derivatives on the Recalcification Time of Plasma.—In view of the hypothetical hazard of thromboembolic sequelae to clinical administration of concentrated platelet material, the effect of such preparations on the coagulation mechanisms in man, specifically on the calcium clotting time, was studied. Minimum recalcification time obtained with platelets preparations and concentrates was found to be of the same order as that of whole blood or plasma, indicating that the clot-promoting activity of platelets material does not constitute a hazard.

The normal clot-promoting activity of platelets appears to be lost at extraordinary high concentrations. Further, as the concentration is increased above normal levels there is an associated prolongation of the recalcification clotting time.

It is concluded that human platelets and their stored, frozen, and lyophilized derivatives do not excessively promote coagulation.

Boletín médico del Hospital infantil, Mexico, D. F.

12, No. 5 (Oct.) 1955

Sodium & Potassium in the Blood Serum of Normal Children. Carmen Suarez and Jesus Kumate.—p. 481.
Traction Forceps for Separation of Bone Fragments. Luis Sierra Rojas.—p. 495.
Generalized Tuberculosis in a Premature. Lazara Benavides V., Luis Rangel, Joaquin Belloc, and Julio Sanchez Acuna.—p. 501.
Cerebral Abscess. Marin Ramos Contrera, Miguel Ramos Murguia, and Luis Duran Romano.—p. 507.
Clinical Pathological Sessions. Maximiliano Salas, M. Antonio Villasana, Higinio Esparza, and Margarita de Pinto.—p. 511.
Dehydration in Infancy. Federico Gomez S., Rafael Ramos Galvan, Silvestre Frink, and Gustavo Gordillo.—p. 531.

Cerebral Abscess.—This is a case history of a 4-year-old boy who had a negative history as an infant except that he had a purulent ophthalmia at birth. Also at 8 months he had a head injury with loss of consciousness for a period of 3 hours. No trouble resulted from this but three years later he had his first tonic-clonic generalized convulsion with loss of consciousness for two or three minutes. After his third seizure he was hospitalized.

There was no fever but severe headache which did not respond to drugs. Reflexes were normal; the gait was not affected. However, he did have the "cracked-pot" sound and mild bilateral papillar edema on examination of the eye grounds.

The laboratory finding showed increased protein in the spinal fluid. Pandy and Norine Appelt tests were positive. Blood serum tests for syphilis were positive but there was no evidence of central nervous system involvement; spinal fluid was negative for lues.

An x-ray of the cranium showed discrete separation of sutures and digital impressions present. The sella turcica was normal. No localization was possible until the pneumoencephalogram of lesion revealed a left parietotemporal lesion. A craniotomy was done, and an intracerebral abscess was opened and 90 cc. of pus removed. There was no bacterial growth from the evacuated pus. Penicillin was used after the evacuation of pus, and the boy and his mother were treated for syphilis. Recovery was complete, and the syphilis is regarded as purely incidental to the lesion.

12, No. 6 (Dec.) 1955

Editorial: Historical Evolution of the Concept of Pathology. Maximiliano Salas M.—p. 591.
Supracotyloid Osteotomy (Technic for Stabilizing Reduction in Dislocation of the Hip). Luis Sierra Roja and Enrique Fernandez.—p. 595.
Subdural Effusions Following Prurulent Meningitis. Lazaro Benavides V., Raul René Molina A., Ramiro Villareal, and Eduardo Cardenas Fajardo.—p. 605.
ACTH and Cortisone in Refractory Cardiac Edema. Rafael Soto Allande, Gustavo Gordillo, M. Apareceda Samparo Zacchi, and Franco Velox.—p. 615.
A Case of Christmas Factor Deficiency. Rafael Soto Allande, Samuel Dorontes Mesa, Olga Castrejon, and Concepcion Velasco.—p. 625.
A Case of Thallasemia Major. Rafael Soto Allande, Samuel Dorontes Mesa, Olga Castrejon, and Concepcion Velasco.—p. 637.
Clinical Pathological Sesaions. Condensed Clinical Histories. Maximiliano Salas, Higinio Esparza, Kurt Ambrosino, and Margarita de Pinto.—p. 651.
Problems in Pediatrics: Pediatric Proctology. Eduard Echevarria and Carlos Mariscal.—p. 673.
Hypospadias. J. Castenado Villa.—p. 685.
Fractures of the Cranium. Miguel Ramos Murguia and Manuel Santos Morales.—p. 693.

Supracotyloid Osteotomy (Technic for Stabilizing Reduction in Dislocation of the Hip).—The author describes an operation to be used on congenital dislocations in older children and in luxations following poliomyelitis. The operation is described in detail

including the use of fragments of refrigerated homologous bone grafts. Spongy bone is preferred. There are excellent diagrams and x-rays of seven cases who had this type of operation.

The purpose of the supracotyloid iliac osteotomy is to lower the acetabular angle. In the cases presented the average correction of the acetabular angle was 19.2 degrees. This operation can be done in combination with other operations such as osteomy of malrotation, conventional cotyloplasty, arthroplasty, alignment osteotomies, acetabuloplasties, and diaphasectomies. The author presents this paper he wants the comments of other orthropedic surgeons. The children have done well, but the author believes more time is needed for proper evaluation.

13, No. 1 and 2, 1956

Argentina: Pediatric Focus on Psychosomatic Illness. Florencia Escardo.—p. 21.

Brazil: Milk Banks. Adamastor Barbosa.—p. 29; Past and Present Day Treatment of Pertussis. Lionel Gouzaga.—p. 35.

Colombia: The Use of Some Vermifuges in Parasitosis. Jorge Camacho Gamba.—p. 43; Federico Gomez, A Life for Children. Juan Zapata Olivella.—p. 53.

Costa Rica: Antimony Compounds Used in the Treatment of Muco-Cutaneous Leishmaniasis in Children. Antonio Pena Chavarria.—p. 57.

Cuba: Hypoglycemia in the Malnourished Child. Arturo J. Aballi.—p. 63; Pathology of Mesenteric and Medrastinal Lymph Nodes in Bacterial Diarrheas in Children. Agustin Castellanos.—p. 73; Acute Renal Insufficiency. Enrique Galan, Aristides Menéndez, Ricardo Portnondo, and Francisco Fernandez Suarez.—p. 81; Intestinal Obstruction in the Newborn. Emilio Soto Pradera, Juan Silverio Latour, José R. Montalvo, and Frederico Fusté.—p. 101; Chronic Massive Eosinophilia. T. Valledor, J. Leon F. Casales, F. Pérez Hurtado, and C. Satonowsky.—p. 123.

Chile: Field Experience in Pediatric Teaching. Arturo Balza Goni.—p. 135; Some Aspects of the Treatment of Acute Nutritional Disturbances in the Infant. Julio Meneghello, Jorge Rosselot, Fernando Monckeberg, and Carmen Aguico.—p. 139.

Guatemala: Miliary Tuberculosis in the Child. Dr. Ernesto Cofino.—p. 159; Comments on the Relation Between Upper Respiratory Infections and Nutritional Disturbances in the Child. Neri Flores R.—p. 177.

Uruguay: Disturbances of Carbohydrate Metabolism in Infants. Luisa Saldun de Rodriguez.—p. 181.

Venezuela: Serological Resistances and Relapses in Congenital Syphilis Treated with Penicillin.—p. 195.

United States of North America: Minimum Recommendation for the Prevention and Control of Infection Among Hospital Newborn Infants. C. D. Cummings; Observations on Amino Acid Metabolism in Malignant Malnutrition (Pluricarencial Syndrome). Nung W. Cheung, Dorothy Fowler, Patricia M. Norton, Selma Snyderman, and L. Emmett Holt Jr., with the assistance of Eileen Hasselmeyer.—p. 217; Management of Acute Severe Illness in Infancy and Childhood. Charles D. May and Robert D. Gauchat.—p. 227; The Chemical Anatomy of Human Skeletal Muscle During Growth. Jack Metcoff, Jorge Martner, Irena Antonowiez, and William Richardson.—p. 233.

Sweden: The Influence of Peptide Bound Calcium and Phosphorous on Bone Calcification in Rickets. Olaf Mellander and Nils Olsson.—p. 243; Factors Precipitating Iron Deficiency in Infancy. Bo Vahequist.—p. 247.

Mexico: Malignant Lymphoma: A Lymphocytoma of the Ileum. Gral Luis Benitez Soto and Joaquin Corres Calderon.—p. 257; Criteria for Surgery in Congenital Heart Malformations. Ignacio Chaves.—p. 265; Changes of Blood Proteins After Intravenous Saline Infusions in Malnutrition and Hepatic Cirrhosis. Leonel Fierro del Rio, Roberto Reynaud Acosta, Carmen Coyotzin Gordillo, Luis Cancino Serna, and Estela Sanchez Quintanar.—p. 277; Circulatory Failure as a Surgical Accident. J. Garcia Ramos.—p. 291; Diabetes and Pregnancy. Salvador Zubiran.—p. 301.

Hospital Infantil de Mexico: Therapeutic Results with *N,N*-di(2-chloroethyl) *p*-amino-phenyl Butyric Acid (CB 1348) in Certain Malignant Tumors in Children. Alijandro Aguirre and Mario Silva Sosa.—p. 215; The New Department for Premature Infants at the Hospital Infantil de Mexico. J. Alvarez de los Cobos, E. Jurado, and Josefina Sagaon.—p. 331; Hepatic Changes in the Malnourished Child. K. Ambrosius Diener and H. Esparza Sandoval; Stenosis of the Biliary Ducts. Francisco Beltran Brown.—p. 263; Carbonic Anhydrase in Typhoid Fever. Lazaro Benavides V., Jesus Kumate, Humberto Segura, Luis Rangel, and Delfina Arrieta.—p. 369; Psychosomatic Manifestation and Allergic Syndrome. Jose Luis Cortés and Silvia Radillo.—p. 381; Gangrene in Infants with Diarrhea. Joaquin A. de la Torre.—p. 391; Astrocytomas of the Nose. Ramon del Villar.—p. 403; Congenital Dislocation of the Knee in Flexion. Juan Farill.—p. 423; Some Aspects of the Pathogenesis of Nutritional Edema. Rafael Ramos, G. Joaquin Cravioto M., Silvestre Frenk, and Judith Vasquez, S.; Incontinentia Pigmenti. Luis Gomez Orozco.—p. 443; Transparietal Splenoportography in a Patient with Portal Hypertensive Syndrome. Carlos Herrera, Julio Manuel Torroella, and Hector Manuel Quintero.—p. 461; Immunity in the Malnourished Child. Jorge Olarte, Joaquin Craviota, and Berma Campos.—p. 467; Respiratory Infections in Children. J. C. Pagola.—p. 473; Genetics in Ophthalmology. Feliciano Palomino Denna and Graciela Navarro.—p. 486; Evaluation of Erythromycin in the Treatment of Diphtheria.—p. 523; Neurological and Mental Complications of Childhood Infections. Marin Ramos Contreras.—p. 531; Nephroblastoma. Maximiliano Salas M.—p. 531; Mafuccis Syndrome (Multiple Hemangiomas with Dyschondiaplasia). Carlos Sarinana, Marcelino Figueroa, and Gonzales Guittierez Trujillo.—p. 585; The Pediatrician and Congenital Dislocation of the Hip. Luis Sierra Rojas, Juan Rosas Barrera, Fernando Camara y Camara.—p. 595; A Study of Nine Cases of Hemophilia. Rafael Soto Allande, Samuel Dorontes Mesa, and Olga Castrejon and Concepcion Velasco.—p. 609; Serum Osmolarity and Electrolytic Equilibrium During Dehydration in Undernourished Children. Rafael Soto Allande, Samuel Doronte

Mesa, and Gustavo Gordillo Paniagua, and Edmundo Tellez Giron.—p. 625; Pott's Disease. Enrique Suarez Velasquez, Gilberto Alcerreca Sanchez, Hector Peon Vidales, and Luis Guerrero.—p. 641; Hernias and Diaphragmatic Eventrations. Eugenio Toussainta.—p. 649; Bone Marrow Changes in Third Degree Malnutrition. Luis Sanchez Illades.—p. 656; A Study of Nine Cases of Hemophilia. Rafael Soto Allande, Samuel Dorontes Mesa, Olga Castrejon, and Concepcion Velasco.—p. 609.

Disturbances of Carbohydrate Metabolism in Infants.—The author discusses the diagnostic procedures necessary to the diagnosis of galactasemia in a child. She also gives the differential diagnosis between this and other disturbances in carbohydrate metabolism.

The first case was reported by Ruess, in 1908, and from that date until 1951 only 14 were described. Since 1951 twenty-two more cases have been reported. The investigations of Caputto and associates in Buenos Aires have stimulated interest in this condition.

In galactasemia, or galactose diabetes, the galactose passes through the liver without any metabolic change. The enzymes which produce metabolic changes in glucose in the liver are galactokinase, diphosphoglucose, and the uridine diphosphate of glucose. If galactose is not metabolized in the liver, it produces deleterious effects on the entire organism, especially the nervous system.

The treatment is a galactose-free diet. The author believes many cases diagnosed as diabetes mellitus are really galactose diabetes, especially those in infancy.

She reports two cases in girls of the same family who had had galactasemia with bilateral congenital cataracts. The youngest was diagnosed early and proper diet caused improvement in vision; later an operation restored her sight.

The author believes there may be some connection between this disease and von Gierke disease, since both are complex and involve the liver primarily, but there may be other endocrine involvement also.

Therapeutic Results with N,N-di(2 Chloroethyl) *p*-Amino-Phenyl Butyric Acid (CB 1348).—This is a report of the results obtained in the treatment of 32 children with CB 1348. Eleven of the children had Hodgkins disease and the others various other malignant tumors. The details of the treatment and results are described. On the whole the children who had CB 1348 had less leukopenia, longer remissions, and fewer side-effects than those treated with this compound and x-ray therapy. The number of cases is too small to draw many conclusions.

Canadian Medical Association Journal, Toronto

75:709-790 (Nov. 1) 1956

* Cat Scratch Fever. C. E. Marshall.—p. 724.
* Hydroceles of the Testicle Complicating Inguinal Hernias. N. Obney.—p. 733.
* The So-Called Pilo-Nidal Sinus. A. A. Klass.—p. 737.

75:885-972 (Dec. 1) 1956

* Coeliac Disease. J. H. Ebbs.—p. 885.
Treatment of Staphylococcal Empyema in Children. D. A. MacKenzie and J. S. McKim.—p. 914.
* Results of Institutional Treatment of Juvenile Mental Defectives Over a 30-Year Period. J. R. Grant.—p. 918.

Cat Scratch Fever.—The author discusses cat-scratch fever clearly and in considerable detail. He reports the occurrence of 11 cases in Nova Scotia. These have been picked up by the routine surgical biopsies in one year.

There are several good illustrations of the pathologic condition. Symptomatic treatment is all that is required in this self-limiting disease. Antibiotics do not seem to have any effect. It is curious that most of the cases occurred in December, suggesting to the author a relationship with the winter habitat of certain birds.

Hydroceles of the Testicle Complicating Inguinal Hernias.—Hydrocele is frequently associated with inguinal hernia. The author reports 1248 cases. In this large group only 61 hydroceles were not associated with inguinal hernia. The hydrocele was commoner on the right side in the ratio of five to three.

A series of 871 cases of hydrocele associated with inguinal hernia was presented. Surgical treatment was reported to be 100% effective in simple hydrocele without hernia and 91.3% effective hydroceles complicated by inguinal hernia. Large hydroceles obscured small inguinal hernias in approximately 60% of such combined cases. Care must be taken at operation to avoid injury to the spermatic cord in order to prevent postherniorrhaphy hydrocele.

The So-Called Pilo-Nidal Sinus.—The author presents a new and critical review of this subject and comes to the following conclusions:

"1. A critical review of the literature reveals that there is very little support for textbook statements concerning the theory of embryonic origin of pilo-nidal sinuses and suppuration.

2. Recent studies indicate that pilo-nidal suppuration is due to a combination of factors in which body build, the postanal dimple, the trauma of broken hairs and problems of local hygiene play an important part.

3. Accumulated experience indicates, furthermore, that pilo-nidal suppuration is a self-limiting disease and that practically no fresh cases are seen after the age of 30."

Coeliac Disease.—The author reviews the clinical picture of coeliac disease with an indication of some of the factors which may contribute to its production. Fat absorption studies indicate that a properly controlled patient should have reasonably normal fat absorption. The absorption of unsaturated fat is better than that of saturated fat. The discovery that the gluten of cereal, particularly wheat, is harmful in some cases has provided an advance in the management of this condition. The author also tested the role of food allergy. The skin tests with protein did not appear to be of any value.

Clinical experience with gluten-free diets, control of infection, the use of special starch recipes, and in severe and resistant cases the judicious use of cortisone, indicates that significant advances in our management of this disease have been made.

Results of Institutional Treatment of Juvenile Mental Defectives Over a 30-Year Period.—This is an interesting review, particularly since it is rather unusual. It is a report of 310 patients discharged from the Provincial Training School at Red Deer, Alberta, with follow-up studies.

The author states that for purposes of investigation treatment is considered successful if the trainee has maintained his or her position in society without conflict leading to official interference. He reports successful discharges in relation to the intelligence quotient. The I. Q. factor is a variable one in predicting successful treatment. Maximum success was obtained with the group who had an I. Q. of 60-69, while significant falling off in success was apparent in the high-grade moron group, I. Q.'s 70-85. In the author's opinion the low-grade morons were patently aware of their defect, accepted it, and were able to effect a realistic adjustment on discharge. High-grade morons were inclined to deny their disability and did not recognize their limitations. High-grade morons spent 1.6 years longer in training in the institution than the low-grade morons and were discharged at an age at least one year younger.

It is stated that the high-grade morons are admitted earlier and have to cope with the entire period of their adolescent emotional development in an atmosphere of "parental rejection," that is, institutionalization. This in itself tends to make compensation for the defect more difficult. The failures with the morons are discussed. Many of them are committed to the Provincial Mental Hospitals. Certain of the males appeared as psychopathic personalities and criminal offenders.

The author notes that the prevalence of character disorder among all but the lowest grade of admissions emphasizes the neurotic accompaniment of mental deficiency in its higher grades. He defines character disorder as "persistent misconduct trying the patience of society, or such that the parents themselves have declared the child beyond control."

He noted that in no case had any male been charged with rape or attempted rape or been involved in any heterosexual offense before admission. On the other hand, a large proportion of females had been concerned in illegitimate births and promiscuity. To the author this indicated that the female defectives were easy prey for the wiles and depredations of "normal" society.

He warns that our understanding of why the mental defective fails in society should not be confined to a knowledge of his I. Q. plus the psychological generalizations currently in vogue. From the medical angle he must remain an individual case as much as any psychiatric case which has its own all-important facets.

The benefit of training is possible in all groups down to and partially including the low-grade imbeciles. There is a prime need for treatment of character disorder which is found to be a common concomitant of juvenile mental deficiency and a main factor in success or failure in borderline or moron groups.

Journal of the American Medical Association, Chicago

162, No. 10 (Nov. 3) 1956

* Treatment of Labial Adhesions in Children. O. W. Anderson.—p. 951.

162, No. 14 (Dec. 1) 1956

Immunization of Infants with Living Attenuated Poliomyelitis Virus. Hilary Koprowski, T. W. Norton, Klaus Hummeler, Joseph Stokes Jr., A. D. Hunt Jr., Agnes Flack, and G. A. Jervis.—p. 1281.
Fetal Mortality in Cesarean Section. Moses Grossman and R. C. Benson.—p. 1289.
Isolation of Echo Virus Type 6 During Outbreak of Seasonal Aseptic Meningitis. D. T. Karson, A. L. Barron, Warren Winkelstein, and Seymour Cohen.—p. 1298.
Diagnosis and Treatment of Eosinophilic Granuloma of Skull. R. S. Knighton and J. D. Fox.—p. 1294.
* Generalized Cytomegalic Inclusion Disease in Newborn Infants. McLemore Birdsong, D. E. Smith, F. N. Mitchell, and J. H. Corey.—p. 1305.

Treatment of Labial Adhesions in Children.—Labial adhesions are not an uncommon finding in the female infant and child. In the earliest reports on this condition it was assumed that the adhesions were congenital. Adhesions, however, have been noted in children who had not had them at birth. The explanation then followed that they followed an inflammatory process in the vulva. This explanation was also shown not to be true.

The author believes that the cause of these adhesions is that the mucus secretions in such girls contains a certain peculiar mucilaginous property that causes these two opposing surfaces to adhere, while in girls with a more fluid type of mucus secretion there is no tendency for adhesions to develop. The author states that symptoms from such adhesions are rare and if such occur will probably be from urination. He suggests that only if symptoms occur should the adhesions be broken.

Generalized Cytomegalic Inclusion Disease in Newborn Infants.—The authors discuss the history, etiology, clinical findings, and treatment of generalized cytomegalic inclusion disease. The salivary gland viruses are the etiological agents of human cytomegalic inclusion disease and of related conditions in many species of animals. The generalized disease in the newborn infant appears to be a primary infection by the virus from either an intrauterine or a postnatal infection. The usual signs and symptoms are jaundice, hepatomegaly, splenomegaly, purpura, thrombocytopenia, and hemolytic anemia. Less frequent findings are intracranial calcifications, cerebral hemorrhage, convulsions, and cyanosis. Late-occurring symptoms include vomiting, diarrhea, failure to gain weight, and chronic eczema.

At the present time the only way to make the diagnosis in the living patient is to find in fresh urinary sediment tubular epithelial cells with the characteristic inclusions. Removal of tissue for histological study, however, may also be done.

Little is known concerning the treatment of this disease except for the fact that cortisone has been of some value and exchange transfusion has been advocated but not yet reported in the treatment.

The authors present the findings of two infants with this disease, one having survived.

The Journal of Pediatrics, St. Louis

49, No. 2 (Aug.) 1956

Amino Aciduria, Congenital Defects, and Mental Retardation. H. E. Thelander and R. Imagawa.—p. 123.
Complications of Smallpox Vaccination and Their Treatment with Vaccinia Immune Gamma Globulin. R. Lundstrom.—p. 129.
The Treatment of Diabetic Acidosis: Comparison of Treatment Regimes With and Without Parenteral Potassium. M. R. Behrer, D. Goldring, and A. F. Hartmann.—p. 141.
Convulsions in Tuberous Sclerosis Controlled by Elimination of Impulses Originating in the Basal Ganglia. H. W. Baird, H. T. Wycis, and E. A. Spiegel.—p. 165.
* Intramuscular Iron for the Treatment of Iron Deficiency Anemia in Infancy. R. O. Wallerstein.—p. 173.
Portal Hypertension in a Child Diagnosed by Splenoportogram. A. I. Kirimli, A. Ertugrul, and S. Levine.—p. 177.
Aneurysm of Thoracic Aorta in an Infant Treated by Resection and Arterial Homograft. D. A. Cooley and F. M. Taylor.—p. 185.
On the Nature of the "Stenosis" in Congenital Hypertrophic Pyloric Stenosis. J. J. Wiener, J. M. McGinley, and D. K. Adler.—p. 191.
Congenital Atresia of the Ileum in Two Brothers. S. T. Winter and M. Zeltzer.—p. 194.

Malignant Thymoma (Lymphocytic Type). J. I. Hudson, F. P. Catanzaro, A. F. Bloodworth, and O. W. Topp.—p. 197.
The Bacterial Flora of the Intestinal Tract: Changes in Diarrheal Disease and Following Antimicrobial Therapy. M. T. Colgan.—p. 214.

49, No. 3 (Sept.) 1956

Congenital Nonspherocytic Hemolytic Anemia. W. Krivit, R. T. Smith, J. F. Marvin, R. Read, and R. A. Good.—p. 245.
How Much Bed Rest Is Necessary for Children with Fever? J. P. Gibson.—p. 256.
Aminophylline (Theophylline Ethylenediamine) Poisoning in Children. B. H. White and C. W. Daeschner.—p. 262.
Incidence of Rheumatic Fever in San Francisco Children. S. J. Robinson.—p. 272.
Poliomyelitis in Pregnancy: Effect on Fetus and Newborn Infant. M. Siegel and M. Greenberg.—p. 280.
Megacolon as a Manifestation of Familial Autonomic Dysfunction. H. J. Grossman, M. A. Limosani, and M. Shore.—p. 289.
Nonparasitic Liver Cysts in Children. P. L. Desser and S. Smith.—p. 297.
* Purpura in Childhood. S. D. Mills.—p. 306.
Parinaud's Oculoglandular Syndrome. W. Pick.—p. 316.
Superior Vena Caval Obstruction in Childhood. J. B. Gillespie.—p. 320.
Duplication of the Terminal Ileum. H. Boyd and M. B. Rubinow.—p. 326.

49, No. 4 (Oct.) 1956

Treatment of Erythroblastosis Fetalis, with Special Reference to Sensitization to Rh-Hr Factors Other Than Rho. A. S. Wiener, I. B. Wexler, and G. J. Brancato.—p. 381.
Cortisone Therapy of Lye Burns of the Esophagus. E. S. Ray and D. L. Morgan.—p. 394.
Reserpine in Cerebral Palsy. R. D. Harris and E. H. Rowley.—p. 398.
Electrolyte Considerations in Exchange Transfusions for Erythroblastosis Fetalis. R. P. Bolande, H. S. Traisman, and H. F. Philipsborn.—p. 401.
Soiling in Children Due to Chronic Fecal Impaction. G. M. Feigen.—p. 407.
Experience in Secondary Screening of Cardiac Suspects of School Age. S. Friedman and C. R. E. Wells.—p. 410.
Prevalence of Heart Disease Among School Children in Israel. M. A. Szabo and L. J. Ross.—p. 417.
Some Blood and Salivary Nonprotein Nitrogen Constituents in Children, and Dental Caries. G. Nikiforuk, S. H. Jackson, M. A. Cox, and R. M. Grainger.—p. 425.
An Evaluation of the Effects of Cerebral Palsy on Dentofacial Development, Especially Occlusion of the Teeth. D. C. Lyons.—p. 432.
Pulmonary Endarteritis with Cor Pulmonale in Infancy. V. Chambers and J. S. Wellington.—p. 437.
Pneumatosis Cystoides Intestinalis in Children. M. Bilger.—p. 445.
Discordant Monozygotic Twins. H. E. Stadler and W. Chroniak.—p. 450.
* Hepatitis in Three Siblings: Possibility of Intrauterine Transmission. A. G. Beard.—p. 454.
Coarctation of the Aorta with Aneurysm and Rupture into the Esophagus. D. Whyte and A. T. Lu.—p. 461.
An Extracranial Varix of the Sigmoid Sinus. P. P. Rickham and H. W. Lipow.—p. 465.
Recent Discoveries in the Etiology of Acute Respiratory Infections: The Adenoviruses. R. Ward—p. 480.
Informing the Parents of the Mentally Retarded Child. H. Bakwin.—p. 486.

Intramuscular Iron for the Treatment of Iron Deficiency Anemia in Infancy.—The author reports on the use of an iron dextran complex (Imferon) for intramuscular use in iron-deficiency anemia. It was given in 1-2 cc. doses, representing 50 to 100 mg. elemental iron. Total dosage depended on age: under 12 months, 200 mg. (elemental iron); 12-24 months, 300 mg.; over 24 months, 400 mg. Dosage was based on average iron content in newborn infants and average annual iron increments in childhood. Injections were given daily into gluteal muscle. There were no local pains, tenderness, redness, or swelling, but slight brownish discoloration was seen in one infant lasting for a week. There were no systemic reactions.

The results of intramuscular iron were prompt; levels of 12 gm. of hemoglobin were reached in all four patients by three weeks. Not all patients had reticulocyte responses, but most did. The response of these iron-deficient anemias in infants was faster by intramuscular injection than by oral intake. With this dosage the indices were normal by three months, indicating that enough iron was given.

The author states that infants may be given 2-3 gm. of iron with impunity and without danger of hemosiderosis or hemochromatosis. If the anemia does not respond, the author believes that the diagnosis was wrong.

Purpura in Childhood.—The author reviews the experience at the Mayo Clinic with purpura. He divides purpura into two groups: (1) thrombopenic and (2) nonthrombopenic. More than half the patients were under 6 years of age; males predominated slightly under 10 years of age, whereas females predominated over 10 years. Of 187 cases, 105 were thrombopenic and 82 nonthrombopenic. It was pointed out that

this incidence was probably misleading because the thrombopenic group were more apt to be referred to the hospital with the question of splenectomy or with serious bleeding.

Thrombopenic purpura: in one-fourth the condition was secondary to infection or acute exanthemas, in three-fourths it was idiopathic (no cause such as drugs, leukemia, etc). Of the idiopathic, one-third were acute and two-thirds, chronic. In three other cases, one was secondary to x-ray irradiation, one was caused by drug intoxication, and one was secondary to reticuloendotheliosis.

Nonthrombopenic purpura (82 patients): 49 had so-called allergic or anaphylactoid purpura; all 49 had bleeding into skin and mucous membrane; 36 had involvement of joints; 30 had visceral bleeding; 18 had hematuria with albuminuria and at times azotemia, and hypertension. Eighteen others had bleeding into the skin during the course of or following an infection. In 13 the defect was considered as vascular. In one it occurred in a child with nephritis and cirrhosis. In one it was due to a chemical and one was diagnosed as congenital thrombasthenia.

Splenomegaly was noted in 21 of the patients with thrombopenic purpura and 10 with nonthrombopenic purpura; the author states that more spleens were found enlarged at operation but that marked splenomegaly is not characteristic of either type of purpura.

Intracranial bleeding occurred in 5 of the 187, all having thrombopenic purpura. Menorrhagia occurred in five adolescents and vaginal bleeding in three younger girls, all having thrombopenic purpura. Hematuria occurred in 18 of the nonthrombopenic purpura, only one of which went on to develop chronic nephritis. Hematuria also occurred in 17 with thrombopenia.

Laboratory differentiation revealed that in thrombopenic purpura platelets were low, megakaryocytes were normal in number but abnormal in function, and tourniquet test was positive.

Prognosis was good. Of 11 deaths, all in the thrombopenic group. In idiopathic group there were four deaths, two from cerebral hemorrhage and two others with uncontrollable bleeding. The other seven died from the underlying cause—three from x-rays or drugs, four with infections.

Treatment: In secondary types of either group look for cause. Use Silicone technique in transfusions. The author feels that steroid hormone therapy is valuable in acute bleeding episodes in patients with thrombopenic purpura. He was disappointed, in general, with this form of therapy, but was not sure the dose of steroids was high enough. Splenectomy was performed in 54 patients with two deaths. Indications were prolonged and severe bleeding; 90% benefited. With medical treatment 84% benefited (of 24 cases) and 2 died.

Hepatitis in Three Siblings: Possibility of Intrauterine Transmission.—The author reports on three siblings who developed hepatitis between ages 2 and 2½ months. The first child had symptoms at 2½ months of vomiting, irritability, jaundice, large tender liver, and light stools. She recovered. The second sibling had a similar, but milder history at age of 2 months. The third sibling (which the author took care of) developed symptoms at 2½ months of jaundice, irritability, dark scanty urine, and acholic stools. This child finally died and autopsy showed almost complete destruction of the normal architectural pattern of the liver. The mother of these children had had hepatitis with jaundice at 13 years of age but could remember no antecedent injections, a transfusion of blood or blood derivatives. The mother and one sibling had a positive cephalin flocculation test.

The author reviews the literature. She refers to two reports which state that mothers suffering from infectious hepatitis during pregnancy deliver normal babies. Viremia in infectious hepatitis is very transient, but in serum hepatitis it is very prolonged. She refers to Stokes' report of a case of a baby who developed hepatitis at 2 months of age and serum from both mother (who was well) and baby produced hepatitis in volunteers, thus lending credence to the possibility that neonatal hepatitis may be due to transmission of the serum hepatitis virus in utero. The author refers to several reports of families with more than one sibling affected with hepatitis in the last few months of life.

Pathologically, a common finding is parenchymal giant cells in the liver. The more fulminating cases show a great deal of necrosis and autolysis. The less fulminating often show focal areas of necrosis and inflammatory infiltration associated with parenchymal giant cells.

In concluding the author states that "it is questionable whether the mother's jaundice in adolescence or a later (inapparent) serum hepatitis should be correlated with her positive cephalin flocculation test and the transmission of hepatitis to her offspring."

Medical Journal of Australia, Sydney, N. S. W.

2, No. 1 (July 7) 1956

Syme Memorial Lecture: Surgery of the Heart, Past, Present and Future. C. J. Officer Brown.—p. 1.
Cat-Scratch Disease in Western Australia: A Report of Three Cases. James R. H. Watson.—p. 20.

2, No. 2 (July 14) 1956

Defective Blood Coagulation Associated with Intrauterine Foetal Death. J. M. Farrar.—p. 65.

2, No. 3 (July 21) 1956

Infant Mortality in Australia. H. O. Lancaster.—p. 100.

2, No. 5 (Aug. 4) 1956

Maternal Understanding and the Physical Health of Babies. Mary McLelland and F. W. Clements.—p. 173.
Eosinophilia with Hepatomegaly. Mona Blanch.—p. 184.

2, No. 6 (Aug. 11) 1956

* Foeto-Maternal Transfusion: Another Cause of Post-Haemorrhagic Anaemia in the Newborn. John H. Colebatch, David Pitt, and T. G. Maddison.—p. 209.

2, No. 7 (Aug. 18) 1956

Gastro-Oesophageal Reflux in Infancy and Childhood. Frieda E. Piarre.—p. 241.
Use of Rhesus-Positive Blood in Exchange Transfusion for Haemolytic Disease of the Newborn. S. E. L. Stening.—p. 246.
A Study of the Anaemia Following Exchange Transfusion in Haemolytic Disease of the Newborn. S. E. J. Robertson.—p. 250.
Febrile Convulsions in Infancy and Childhood. Wilfred Cary.—p. 254.
Medical Societies: Report of Meeting of Australian Paediatric Association.—p. 272.

2, No. 8 (Aug. 25) 1956

A Case of Congenital Spherocytic Anaemia with an Aregenerative Crisis. D. White.—p. 302.

Foeto-Maternal Transfusion: Another Cause of Post-Haemorrhagic Anaemia in the Newborn.—The authors define anemia of the newborn and state that one can usually accept the hemoglobin of less than 16-17 gm. as definitely indicating this condition. These are figures for peripheral blood. Approximately 5% of the cases are not due to erythroblastosis fetalis. Among the etiologic factors of this 5% is the inapparent hemorrhage from the fetal surface of the placenta into the mothers circulation. A report of three cases is given. The findings in the infants are classically (1) pallor, (2) weakness and loss of tonus, (3) tachycardia, (4) lack of jaundice, and (5) dramatic response to transfusion. Important negative findings are lack of hepatomegaly and splenomegaly.

Erythroblastosis can be ruled out by a knowledge of the family history, the mothers blood group, and the Coomb's test.

The diagnosis of fetal maternal transfusion can be established by finding in the mother's blood an abnormally high concentration of fetal hemoglobin. In normal adults this concentration is from zero to 1.7%. In the three mothers reported the amount of fetal hemoglobin was well over 2%, and the time after delivery in which these values were found varied from a few days to six weeks. The authors believe that the diagnosis of this condition probably has been frequently missed owing to lack of knowledge of its existence. Treatment consists of transfusion.

Minerva pediatrica, Torino

8, No. 9 (March 3) 1956

Twenty-Five Years in the Treatment of Three Thousand Premature Infants. M. Ortolani and E. Vallisneri.—p. 215.
Changes in the Coagulation of the Blood as the Result of Viral Hepatitis. M. Crisalli and G. Cotellessa.—p. 235.
° The Use of ACTH Intradermally, Together with Chloramphenicol, in the Treatment of Typhoid Infections. E. Segagni and P. Nicola.—p. 241.
An Electrophoretic Study of the Serum Proteins in Measles. E. Tosi and G. Biscioni.—p. 257.
The Use of Preparation of Chloramphenicol and a Balsam-like Substance in the Treatment of Bronchopneumonia in Children. U. Widmer and M. P. Bolgiani.—p. 259.

8, No. 11 (March 17) 1956

The Prognostic Value of Determinations of Pyruvic Acid in the Spinal Fluid of Patients with Tuberculous Meningitis. G. Cafferena and M. Merlini.—p. 303.
° The Effect of Cortisone on Vaccinia Inoculations in the Rabbit. M. Crisalli and A. Terramagna.—p. 311.
The Agglutination Titer of the Serum, and Placental Transmission of Anti-Typhoid Agglutinins from Mother to Fetus, When the Former Was Receiving Thyroid Therapy. E. Segnani.—p. 317.
The Lipoprotein Curves of the Serum After the Administration of Vitamin B12 to Children Receiving High Fat Diet. G. Gelli and L. Pardelli.—p. 320.
The Rehabilitation of Infants with Paralytic Poliomyelitis. G. Poli and M. Valle.—p. 325.

8, No. 12, (March 24) 1956

The Diagnosis of Thalassemia: Investigations as to Hemoglobin Formation. S. Barberi.—p. 342.
The Lung Pathology Due to Viruses and Rickettsiae in Premature Infants. D. Gaburro.—p. 345.
° Precocious Pseudopuberty in a 2 Year Old Girl Due to the Use of a Pomatum Containing Estradiol. G. Brogi.—p. 351.
The Etiology of Interstitial Plasm Cell Pneumonitis in the Premature Infant: Some Results in Prophylaxis by the Use of Ultra Violet Rays. C. Torricelli.—p. 356.

8, No. 19-20 (May 19) 1956

Urography in Infants Using a Tri-Iodate as the Contrast Medium. B. Carlotti and L. Papagni.—p. 709.
° Meningitis Due to the Escherichia Coli in the Newborn. P. N. De Sario and P. Nicola.—p. 712.
Cardiac Catheterization. E. De Langlade.—p. 723.
A Case of Miliary Tuberculosis in Which There Was a Relapse. G. Ruttini and A. Manna.—p. 731.

The Use of ACTH Intradermally, Together with Chloramphenicol, in the Treatment of Typhoid Infections.—Eleven children, 10 months to 8 years of age, nine of them with typhoid fever and two with paratyphoid fever, were under treatment with chloramphenicol. Then ACTH was also given for from 7 to 11 days in daily doses of 3 to 6 mg. intradermally. The clinical results of the ACTH therapy were very favorable, especially in relieving the prostration, fever, vomiting, and diarrhea. Many laboratory studies were made in this study. The white blood count and the sedimentation rate tended to approach normal values. The ACTH was found to depress the titer of the Widal reaction, but did not at the same time lower the gamma globulin of the blood serum. The authors caution that the ACTH should not be given for over 10 days because of the "proinfectious" action of the drug.

The Effect of Cortisone on Vaccinia Inoculations in the Rabbit.—The vaccinia reaction in rabbits who received cortisone injections five days after inoculation was the same as in control rabbits which had received no cortisone. However, when the vaccination was done at the same time as cortisone was given, the pustule formation was minimal in size or entirely absent; all of these rabbits died; in some the death was preceded by paralysis.

Precocious Pseudopuberty in a 2 Year Old Girl Due to the Use of A Pomatum Containing Estradiol.—A 2-year-old girl weighed 28½ lb., was 34 in. tall, and had all 20 of her deciduous teeth; the breasts were enlarged to the size of a mandarin, and the nipples stood out and were pigmented; the labia were enlarged and pigmented; suprapubic hair was beginning to be noticeable. The cause of the precocious sexual development appears to have been the use some months previously of a pomatum containing estradiol for a vaginitis in the child.

Meningitis, Due to the Escherichia Coli, in the Newborn.—Three cases of meningitis due to the Escherichia coli are reported in newborn infants; one child died within a few days, the second developed hydrocephalus and was in hopeless condition after

3 months, while the third recovered completely. The infecting organisms in the first case was E. Coli O 111:B4, and in the other two E. Coli O 26:B6. The organisms were all sensitive to streptomycin and chloramphenicol, while two were sensitive to Aureomycin and Terramycin, and none to penicillin; it is therefore apparent that tests for sensitivity are important for proper therapy. The literature reveals that 35% of the meningitis cases in the newborn are due to coliform organisms, the mortality rate being very high (about 85%). It appears that the infections are probably "connatal", i. e., associated with the birth.

Monatsschrift für Kinderheilkunde, Berlin

104:224-258 (May) 1956

Studies of the Biology of Human Breast Milk: Decrease in Bacterial Content After Dry Freezing. Carl-August Sager.—p. 224.
* Sabin-Feldman Dye Test Studies of Toxoplasmosis in Children. J. Paul.—p. 228.
The Use of Aspiration in the Resuscitation and Treatment of Premature Infants. Harold Thomas.—p. 236.
Newer Concepts in the Raising of Weakly Premature Infants. Herbert Gross.—p. 244.
Bromide Intoxication in Childhood. H.-J. Rohwedder and D. Pribilla.—p. 247.
Review Article: Rheumatic Diseases. E. Stoeber.—p. 251.

104:259-294 (June) 1956

Studies of the Pathogenesis of Parenteral Dyspepsia and Intoxication in Experimental Animals. Karl Stenger.—p. 259.
The Formation of Urinary Calculi with Cerebral Illness. Guenther Janssen.—p. 270.
Does Fluoridation Provide Protection Against Rickets as Well as Against Dental Caries? H. Gebauer.—p. 274.
The Treatment of Juvenile Diabetes Mellitus: Excretion of Glucose and Renal Threshold in Diabetes of Infants. Johanna Walter.—p. 278.
* Sabin-Feldman Dye Test Studies for Toxoplasmosis in Children. J. Paul.—p. 281.

104:294-334 (July) 1956

Transfer of Lues Reagins Across the Placenta Without Leutic Infection of the Fetus. Walther Furmann.—p. 295.
Cerebral Damage After Burns. Ulrich Huschke.—p. 300.
Determination of Residual Volume by Means of Chest X-Ray. H. Wissler and H. Wierzejewski.—p. 307.
* Frequency of Contact Infection in Poliomyelitis (Institutional Outbreak). Hilt Lennartz and Bernward Rohde.—p. 311.
Diagnosis and Differential Diagnosis of Wilson's Disease. H. Gastagen and W. Spiel.—p. 314.
The Significance of Respiratory Tract Catarrh and Bacterial Allergy in the Pathogenesis and Treatment of Bronchial Asthma in Childhood. I. Radnoti-Recht.—p. 319.
The Tendency Toward Interstitial Pneumonia in Premature Infants. Peter-Heinz Koecher.—p. 322.
Review Article: Tuberculosis. A. Wunderwald.—p. 329.

Sabin-Feldman Dye Test Studies of Toxoplasmosis in Children.—Between June, 1950, and March, 1955, the Sabin-Feldman Dye Test was performed on 635 infants and children up to 3 years of age; 464 patients were more than one-half year old. They were divided into three groups: (1) 95 patients with postencephalitic and other cerebral manifestations of unclear etiology which appeared to be "congenital"; (2) 30 patients with known infectious or toxic diseases of the central nervous system, such as post-vaccinal, pertussis, and measles encephalitis, tuberculous meningitis, etc.; (3) 339 patients with illnesses other than of the central nervous system, serving as controls. The 171 patients less than 6 months of age were not included in three groups, since it was impossible to differentiate transplacental toxoplasma antibodies from those formed actively by the infant. Titers of 1:32 or above were considered positive.

A 25% higher incidence of positive tests was found in Groups 1 and 2 than in Group 3. Of these positive tests almost 70% were more than fivefold increases in Group 1 and more than 20% in Group 2.

It was concluded that in late infancy and early there exists an etiological relationship between serologically diagnosed toxoplasma infection and the postencephalitic syndrome.

It is possible that unnoticed toxoplasma encephalitis may serve as a predisposing factor for the development of secondary central nervous system complications with various infectious diseases.

Sabin-Feldman Dye Test Studies for Toxoplasmosis in Children.—Between June, 1950, and March, 1955, Sabin-Feldman Dye Tests for toxoplasmosis were performed on 286 children between the ages of 4 and 6 years. They were divided into three groups:

(1) 47 children with postencephalitic and other cerebral manifestations of unclear etiology thought to be congenital; (2) 19 with known infectious and toxic central nervous system diseases, such as postvaccinal and measles encephalitis and tuberculous meningitis. (3) 220 with noncentral nervous system diseases. Dye tests were considered positive when titers were 1:32 or above.

It was found that the average percentage of positive tests in Group 1 was five times higher than in Group 3. During the 4th year of life the increase was fourteenfold, during the 5th year three and one-half fold, during the 6th year threefold; 75% of the positive tests were found during the 4th year of life, 23% during the 5th and 6th. During the 4th year of life the percentage of positive tests was six times that of negative tests, during the 5th and 6th years only three times.

In Group 2 the percentage of positive tests was about six times as high as in Group 3. During the 4th year of life the percentage of positive tests was four times higher than negative tests and five times higher in the 5th and 6th years of life.

Comparison of studies between older infants and the 4- to 6-year-old group led to the conclusion that an etiological relationship exists in the 4th year of life between serologically diagnosed toxoplasmosis and postencephalitic manifestations. The possibility exists that undiagnosed toxoplasma encephalitis may pave the way for the development of central nervous system disease secondary to various infectious illnesses.

Differences in interpretation of results obtained in the younger age groups was confirmed indirectly by the results in Group 3 which served as control: percentage of positive tests in this group was six times higher in the 4- to 6-year-old persons than in the older infants. During the 4th year of life the percentage of positive tests was 2.14% higher, and it was 7.93% higher during the 5th and 9.37% higher during the 6th year of life.

These results speak for postnatally acquired toxoplasmosis during these age groups, usually running a latent course. They throw doubt on the diagnosis of congenital toxoplasmosis on the basis of serologically positive tests between 4 and 5 years of age.

Frequency of Contact Infections in Poliomyelitis (Institutional Outbreak).—During September, 1953, an epidemic of poliomyelitis occurred in a children's institution near Bremen, Germany. At that time there were 66 children living there, ranging in ages from 6 months to 3 years. Paralytic poliomyelitis was diagnosed in 14 patients, one of whom died. Brunhilde type was found to be the causative agent in this outbreak.

Two weeks after the appearance of the first paralytic case, 80% of the healthy children in the institution were found to have virus in their stools whereas only two of the adult contacts were found to have virus in their stools. Viremia without clinical illnesses was ascertained in one child who was excreting polio virus in the stool but had not yet developed antibodies.

At the end of the second incubation period most of the children were excreting virus in their stools and had neutralizing antibodies in their sera. Following another three weeks they all had increases in antibody titers of the neutralizing type despite lack of clinical illness. Complement-fixing antibodies, however, were not found as frequently and increases in titer were noted only occasionally.

New England Journal of Medicine, Boston

255, No. 8 (Aug. 23) 1956

Clinical Diagnosis of Aortic Valve Disease. R. Gorlin and R. B. Case.—p. 368.
Salt-Losing Nephritis: Review and Report of Case. A. H. Levere and L. G. Wessum.—p. 373.
Management of Pyelonephritis (Concluded). H. A. Derow.—p. 379.
* Poliomyelitis Vaccination in Southwest Massachusetts in 1955: Influence of a Single Dose of Salk Vaccine. F. R. Philbrook and T. H. Ingalls.—p. 385.

255, No. 9 (Aug. 30) 1956

Zinc Metabolism in Hepatic Dysfunction: I. Serum Zinc Concentrations in Laennec's Cirrhosis and Their Validation by Sequential Analysis. B. L. Vallee, W. E. C. Wacker, A. F. Bartholomay, and E. D. Robin.—p. 403.
* Polyneuritis In Systemic Lupus Erythematosus: Review of the Literature and Report of a Case. L. Scheinberg.—p. 416.
Medical Progress: Pathology: Diseases of Bone. L. Lichtenstein.—p. 427.
Iodide "Mumps" After Intravenous Urography. R. M. Sussman and J. Miller.—p. 433.

255, No. 12 (Sept. 20) 1956

Identification and Significance of Platelet Antibodies. J. L. Tullis.—p. 541.
Medical Progress: Neurology (Concluded). W. K. Jordan and H. H. Merritt.—p. 563.
Editorial: Retrolental Fibroplasia: A Chronologic Review.—p. 580.

Poliomyelitis Vaccination in Southeast Massachusetts in 1955: Influence of a Single Dose of Salk Vaccine.—The authors report on a specific area in Massachusetts, five contiguous townships; furthermore, they are evaluating the ability of a single dose of Salk vaccine to protect children from 6-8 years in July, August, and September. This study was aided by the fact that a good many parents in these towns had adopted a wait and see attitude rather than have their children immunized.

For statistics the authors used the reports to the Boards of Health (data was checked for accuracy), the school census reports for the ages and numbers of children in the communities, and standard inoculation records for the ages and numbers of vaccinated children.

There were seven cases of poliomyelitis among 4270 children inoculated with one dose. Of these six were nonparalytic and one was bulbar. This gave a rate of 164 cases per 100,000. The rate for nonvaccinated children was 774 per 100,000 (18 nonparalytic, 7 paralytic, and 13 bulbar), among 4910 children of the same age group. These figures are based on clinically recognized cases.

As far as safety was concerned, the authors found that the shortest time interval between vaccination and a case of polio was 7½ weeks. They concluded that one dose of the vaccine was both effective and safe.

Polyneuritis In Systemic Lupus Erythematosus: Review of the Literature and Report of a Case.—The author states that, although neurological symptoms are common in the course of systemic lupus erythematosus, only a few well studied cases of associated polyneuritis have been reported. The author reviews the literature and adds a case.

The author's case was an 18-year-old girl who had the typical clinical, laboratory, and autopsy findings of systemic lupus erythematosus. Symptoms of polyneuritis developed early in this patient, even before most of the typical clinical and laboratory findings became apparent. This patient had an elevated pressure and elevated protein of the spinal fluid (270 mg. at beginning with increase to 535 mg/100 ml.). Pathologically, the involvement of the peripheral nerves was largely a collection of amorphous material separating the connective tissue fibers of the involved covering. The author favors the hypothesis that, in his case, the polyneuritis was due to compression of the nerves by this material. He points out that large nerve-fiber types carrying proprioceptive and motor impulses are most susceptible to damage by compression, and his patient's involvement was largely of this type.

Identification and Significance of Platelet Antibodies.—The author points out the two general types of thrombocytopenia: (1) due to the development of antiplatelet immune antibodies (as in many cases of idiopathic thrombocytopenic purpura and hypersplenism) and (2) secondary to deficient platelet production (as in metastatic cancer, leukemia, radiation, etc.). The importance of recognizing the two groups is in the therapy. The second group would respond well to platelet transfusions, whereas the first group might be made worse. The first group responds best to steroid therapy, or splenectomy or both.

A test is described which does not require much equipment but does require meticulous attention to technique. It is essentially testing an unknown serum (antibody) against a standard platelet suspension with complement. When positive there is more than a 5% reduction in platelet count at 90 minutes.

General results were as follows: In nonthrombocytopenic purpura and in normals the test is negative. In idiopathic thrombocytopenic purpura 57% (of 73 cases) of all sera were positive. In hypersplenism 66% (of 14 cases) were positive. In the last two groups treatment by steroids or splenectomy or both did not necessarily revert the test to negative in spite of the clinical improvement and could not be used as a criterion for response. Infectious mononucleosis was also found occasionally to produce antiplatelet antibodies. In congenital purpura 10 of 16 mothers who had babies with purpura showed antibodies. Six of the 10 positives had no clinical purpura. Of 12

infants with congenital purpura 8 of 12 had positive tests. Two types of neonatal purpura are postulated: one, in which mothers never had purpura and an isoimmunization (similar to erythroblastosis) has occurred and, two, in which mothers had had purpura and had antibodies and these are transferred. More than 50% of either type clears up spontaneously at 3 months. Of eight patients with acquired hemolytic anemia and thrombopenia, five had positive tests.

Numerous tests on secondary thrombopenic purpura gave negative tests quite consistently. As a matter of fact, the author believes that the finding of a positive test in an obscure case of thrombocytopenia can be considered strong presumptive evidence that the patient does not have leukemia or metastatic cancer.

By chemical testing, electrophoresis, and testing of eluates from various portions of the protein fraction, the author demonstrated that the active material in the test was in the gamma-globulin fraction.

Pediatrics, Springfield, Ill.

18, No. 4 (Oct.) 1956

Endocardial Fibro-Elastosis: I. Endocardial Fibro-Elastosis Associated with Congenital Malformations of the Heart. D. H. Andersen and J. Kelly.—p. 513.

Congenital Endocardial Fibro-Elastosis: II. A Clinical and Pathologic Investigation of Those Cases Without Associated Cardiac Malformations Including Report of Two Familial Instanecs. J. Kelly and D. H. Andersen.—p. 539.

Electroencephalographic Studies on Children Having Measles with No Clinical Evidence of Involvement of the Central Nervous System. H. J. Grossman, E. L. Gibbs, and H. W. Spies.—p. 556.

Taussig-Bing Complex Associated with Anomalous Right Subclavian Artery Arising Proximal to Coarctation of the Aorta. D. L. Alcott, P. Sanfilippo, and J. E. Edwards.—p. 561.

Progeria: Report of a Case with Cephalometric Roentgenograms and Abnormally High Concentrations of Lipoproteins in the Serum. I. M. Rosenthal, I. P. Bronstein, F. D. Dallenbach, S. Pruzansky, and A. K. Rosenwald.—p. 565.

Salicylate Intoxication. H. D. Riley Jr. and L. Worley.—p. 578.

Candida Infections in Children with Neoplastic Disease: Influence of Therapy with Antibiotics and Steroid Hormones. W. D. Winter Jr. and G. E. Foley.—p. 595.

* Symptomatic Hyponatremia in Acute Infections of the Central Nervous System. W. L. Nyhan and R. E. Cooke.—p. 604.

A Difference in Mortality Rate and Incidence of Kernicterus Among Premature Infants Allotted to Two Prophylactic Antibacterial Regimens. W. A. Silverman, D. H. Andersen, W. A. Blanc, and D. N. Crozier.—p. 614.

Special Article: Maternal Deprivation. K. Glaser and L. Eisenberg.—p. 626.

Review Article: Treatment of Acute Leukemia. J. H. Burchenal, M. L. Murphy, and C. T. C. Tan.—p. 643.

Commentary: Oral Insulin-Sparing Sulfonamides.—p. 661.

Clinical Conference: Ulcerative Colitis. F. H. Wright and J. F. Kenwood.—p. 663.

Symptomatic Hyponatremia in Acute Infections of the Central Nervous System.—Studies of changes in electrolyte concentrations in the serum of five patients with meningitis or encephalitis are reported, and these findings are correlated with characteristic clinical manifestations. These children were found to manifest a significantly low serum sodium in the range of 115-125 mEq. per liter occurring early in the course of the disease and accompanied by signs of water intoxication, namely, restlessness, irritability, convulsions, and coma. Administration of electrolytes in sufficient quantity to correct the deficits was noted to produce consistent alleviation of these manifestations.

The possible mechanisms for the above derangements are discussed in some detail, and it is pointed out that an excessive reduction of water rather than loss of sodium is most likely and that the most probable mechanism is that of excessive production of antidiuretic hormone by the pituitary. Speculation concerning the factors responsible for this excess release of ADH is offered.

Early studies of the electrolytes in the serum of patients with acute infections of the central nervous system is urged. Suggested treatment of hyponatremia on this basis is the intravenous administration of approximately 3 mEq. Na Cl per kilogram of body weight (6 ml. of 3% saline per kilogram) over a two-hour period. It is felt that the addition of potassium to the saline solution is probably important.

La presse médicale, Paris

64 (Aug. 25) 1956

* Dyslexia and Dysorthography. Michel Dugas.—p. 1435.

64 (Oct. 3) 1956

* Novobiocin: Experimental Activity "in Vitro" and "in Vivo": Its Use in Severe Staphylococcic Infections. Réne Martin, Y. Chabbert, and B. Sureau.—p. 1597.

64 (Oct. 10) 1956

* Notes of Practical Medicine: May the Treatment with Radioactive Iodine Give Rise to Leukemia? L. Rouques.—p. 1641.

64 (Oct. 13) 1956

* Two Cases of Streptococcic Endocarditis Treated with Oral Penicillin V. R. Martin, Y. Chabbert, B. Surear, and E. Cayla.—p. 1655.

Dyslexia and Dysorthography.—Dyslexia was first described in 1881, and since that time considerable literature has accumulated on the subject. The clinical picture is that of a child with normal senses, normal intellectual level, absence of preexisting affective disturbances, and a specific disability in learning to read and write. According to the child's age, the school problem varies. There are often associated disorders concerning lateral dominance, left-right orientation, difficulties in spatial organization, deficiencies in the perception of rhythm, and quite often speech disturbances with many of the children learning to speak late, continuing baby talk for a long time, having trouble with articulation of certain consonants, and showing a poverty of vocabulary. Dyslexic children may show only parts of the general picture. No ideologic factor outside of heredity which has been clearly implicated by Hallgren has been found to have any bearing on the problem on congenital dyslexia. The EEG is usually normal and one finds no anoxic insult in infancy. One pair of identical twins with dyslexia has been reported. Children with this disability have shown emotional difficulties in 58%, principally reactive, introvertive, and regressive. Therapy consists in starting from the beginning again and using visual, auditive, and kinetic stimuli to teach the correspondence between the image of the letter and the sound which characterizes it. This then is repeated for the syllables and finally for words. Writing may be retaught in the same manner. The situation must be explained to the parents, and the child must not be blamed. Many children may be greatly helped in two or three months; others require a year or more.

Novobiocin: Experimental Activity "In Vitro" and "In Vivo": Its Use in Severe Staphylococcic Infections.—The authors review the use of Novobiocine, which is an antibiotic active against Gram-positive organisms, and particularly against Staphylococcus. Staphylococci become resistant to Novobiocine, but cross resistance with other antibiotics does not occur. It is most active in an acid medium and is inactivated by serum and an alkaline pH. It is bactericidal, and when used with the Aureomycin group of antibiotics it gives an additive bacterial static affect, while with streptomycin and penicillin it has a synergistic effect. The authors report a severe case of staphylococcic endocarditis in which Aureomycin and streptomycin failed but the use of penicillin and Novobiocine resulted in a cure. Doses of 2 gm. per day resulted in blood levels of 42.7γ per cubic centimeter, similar to those obtained by other authors.

Notes of Practical Medicine: May the Treatment with Radioactive Iodine Give Rise to Leukemia?—The author reviews from the literature the occurrence of leukemia following use of iodine^{131} for cancer of the thyroid and for hyperthyroidism. In all, 7 cases have been reported, but one author who reported 2 cases of leukemia had treated only 16 cases of thyroid cancer. The author concludes that the possibility of leukemia developing should not prevent the use of radioactive iodine in patients with cancer of the thyroid, but it is possible that the risk of leukemia is entirely too high for the use of radioactive iodine in a nonfatal disease like hyperthyroidism.

Two Cases of Streptococcic Endocarditis Treated with Oral Penicillin V.—Penicillin V, orally administered in high doses (12,000,000 units per 24 hours), resulted in blood levels of 4-10 units per cubic centimeter. A 47-year-old man treated by the authors for

27 days with penicillin V alone suffered a small cerebral embolism following which the treatment was changed to intravenous penicillin G and streptomycin. After a total treatment of two and one half months, cure was achieved. A second case, a man aged 28 with streptococcic endocarditis, was treated for 14 days with oral penicillin V and appeared to be doing well but died suddenly of an embolic accident. At autopsy masses of Gram-positive organisms were found in the cardiac fibrinous exudate but could not be cultured. The authors believe that treatment of streptococcic endocarditis by oral penicillin V, especially in association with streptomycin, offers great promise but suggest that anticoagulant should perhaps also be used.

Radiology, Syracuse, N. Y.

67, No. 3 (Sept.) 1956

* Anomalous Course of Left Pulmonary Artery with Respiratory Obstruction. M. H. Wittenborg, T. Tantiwongse, and B. F. Rosenberg.—p. 339.
Ossification of the Pubic Bones at Birth. J. Caffey and S. H. Madell.—p. 346.
Cervical Disk Calcification in Childhood. W. G. Peacher and R. P. Storrs.—p. 396.
* Use of Roentgen Rays to Establish the Identity of Interchanged Infants. S. H. Macht.—p. 404.
* Aeration of the Respiratory and Gastrointestinal Tracts During the First Minute of Neonatal Life. A. G. Boreadis and J. Gershon-Cohen.—p. 407.
Roentgen Demonstration of Gas in the Fetal Circulatory System, a Valuable Sign of Fetal Death. L. S. Ellenbogen, H. Bayer, and M. Gottlieb.—p. 410.
Scurvy Following Folic Acid Antagonist Therapy. J. M. Dennis and Raul Mercado.—p. 412.

67, No. 4 (Oct.) 1956

* Traumatic Torsion of the Lung: Case Report. R. E. Parks.—p. 582.
Roentgenographic Examination of Infant in an Incubator. R. M. Towman, L. Davis, and H. K. Silver.—p. 584.

67, No. 5 (Nov.) 1956

* Congenital Biliary Atresia with Emphasis on the Skeletal Abnormalities. E. J. Levin.—p. 714.
* Familial Fibrous Swelling of the Jaws (A New Case). P. Riley, O. Stuteville, and R. C. Brown.—p. 742.

Anomalous Course of Left Pulmonary Artery with Respiratory Obstruction.—Two patients, ages 3 months and 3 weeks, respectively, observed during life and at necropsy were found to have a left pulmonary artery passing posterior to the trachea.

Symptoms were first observed soon after birth and consisted of cyanotic spells, intermittent wheezing, substernal retraction, and stridor. The clinical picture while not unlike that of a double aortic arch, differed from extrathoracic obstructive lesions, such as congenital laryngeal stridor, in that there was predominantly expiratory wheezing instead of a true inspiratory stridor. The symptoms resembled those of any intrathoracic or major bronchial obstructive lesion which had in common inspiratory and expiratory wheezing with pulmonary emphysema, either general or unilateral. Emphysema, along with narrowing of the trachea below the level of the aortic arch, may be demonstrated on chest roentgenograms. Also an anterior indentation of the esophagus may be a diagnostic sign. Confirmatory evidence is offered by films with opaque oil in the trachea. Bronchoscopy reveals narrowing of the trachea, carina, right main bronchus, or left tracheal deviation.

Of the five cases (all males), three in previous reports and the two of the authors', only one which had been corrected surgically by Potts has survived. The surgical correction of this deformity is an added incentive to pursue specific diagnoses and encourage vigorous therapy.

In response to questions about the present condition of the surviving patient, this reviewer received the following statements from Dr. Potts:

"'The Case of Anomalous Left Pulmonary Artery Causing Obstruction to the Right Main Bronchus' which was published in the *Journal of the American Medical Association*, August, 1945, has been eminently successful. We have seen the child a number of times and the youngster is perfectly well. Both lungs are normally expanded and the child is completely free of symptoms. Mediastinal structures returned to the midline."

Use of Roentgen Rays to Establish the Identity of Interchanged Infants.—An interchange of newborn babies occurred in a hospital under circumstances where the usual laboratory evidence failed to identify two girls. Both mothers had type "O" blood and

both fathers type "A." All were Rh positive. Fortunately one child had had chest x-rays previously, and showed a prominent thymic shadow on the right and five ossification centers in the sternum. After the mix-up chest films showed these changes present in one, not in the other. Also one child had no visible shadow in the lungs and there were only three ossification centers in the sternum. Identification was thus established.

Aeration of the Respiratory and Gastrointestinal Tracts During the First Minute of Neonatal Life.—Roentgenograms of the respiratory and alimentary tracts of 25 infants were made between 25 and 60 seconds after birth. Air was seen in the lungs of all infants, but only 13 had gas in the stomach or intestinal tract. These findings do not agree with previous opinions based on necropsy findings that air is drawn into the esophagus, stomach, and lungs simultaneously. Breslau's test, used in forensic medicine to show whether or not a child has been born alive, depends upon whether the stomach and intestines float in water and is therefore misleading if applied to infants dying within the first minute after birth.

Traumatic Torsion of the Lung: Case Report.—A 7-year-old white girl fell from a moving vehicle and a front wheel passed over the lower chest anteriorly. A chest roentgenogram showed linear densities extending from the left hilum upward and outward toward the apex. The involved lung field became completely obliterated by a homogeneous shadow in two days. This was thought to represent a pressure hemothorax. Eventually a pneumonectomy was undertaken, and the lung was found to have rotated 180 degrees in a clockwise direction on a horizontal axis when viewed from a lateral aspect. The lung, with the exception of the superior segment of the left lower lobe, was resected. The child made a complete recovery.

The early x-ray appearance, age, type of trauma, and lung involved were similar to that of a previously reported case.

While not pathognomonic, the linear shadows on the chest roentgenogram observed in both cases following severe trauma should definitely suggest torsion of the lung.

Congenital Biliary Atresia with Emphasis on the Skeletal Abnormalities.—Severe hepatic damage produces polyclinical abnormalities. There has been no clear distinction between two varieties of osseous dystrophy found in this condition. Two cases with jaundice from birth and esophageal varices are described in detail, each representing a different type of bone change. The first was indistinguishable from deprivation rickets; the second may represent the effects of a combined vitamin A and vitamin D deficiency.

Case 1 showed severe rachitic changes with genu valgum. Coarse demineralization, deep epiphyseal cartilage, and cupping and fraying were present in the bones, even after the vitamin D intake was increased to 50,000 units daily.

Case 2 showed hypomineralization and a ground-glass appearance with "growth arrest" lines. The bones were short, and the diaphyses were under-tabulated. The medullary cavity was widened, and the zone of provisional calcification was marked by a thin sharp line. The epiphyseal cartilages were narrow. There was no bowing of the long bones. The subperiosteal hemorrhages of scurvy and the subperiosteal osteoclastic resorption of hyperparathyroidism were not present.

The treatment of the osseous lesions has been unsatisfactory and a constant response not obtainable, even in the same patient. Aqueous vitamins A and D parenterally in huge doses is probably the best treatment. Surgery offers the only cure for biliary atresia. This is possible in approximately 16% of cases.

Familial Fibrous Swelling of the Jaws (A New Case).—A 5-year-old white boy with wide jaws presented a "squirrel-cheek" appearance which showed multilocular cysts involving the markedly enlarged mandible, with the exception of the condylar processes. Also, the upper jaw was markedly enlarged, encroaching upon the maxillary sinuses. The teeth had rudimentary roots and were poorly aligned, and the dental follicles were irregularly placed and abnormal in size. A skeletal survey disclosed no other lesions.

A biopsy of the jaw revealed loosely arranged whorls of fibrous tissue, with occasional giant cells. Decalcified sections showed trabeculae of normal thickness with connective tissue filling the intervening spaces. There was an occasional area of proliferating bone, with some increase over the usual number of osteoblasts.

While the microscopic findings were typical of fibrous dysplasia, the fact that the father and uncle had apparently similar changes in their youth, favors a familial occurrence. Also the diffuse involvement of the maxillae and mandible indicate, in the author's opinion, that this was another example of "familial fibrous swelling of the jaws," the 10th to be recorded.

Correspondence

HYPOKALEMIA

To the Editor: Drs. A. L. Skinner and F. C. Moll presented a report on "Hypernatremia Accompanying Infant Diarrhea" in the December issue of the A. M. A. JOURNAL OF DISEASES OF CHILDREN (Vol. 92:562 [1956]). A surprisingly large number of their patients developed edema, paralysis, and convulsions; two of their twelve patients died.

It was not pointed out that five out of six patients in whom serum potassium analyses were made had hypokalemia. It would appear that potassium deficiency could not be excluded as a component in the symptomatology of some of their patients.

HANS KEITEL, M.D.
Philadelphia

News and Comment

ANNOUNCEMENTS

American Foundation for Allergic Diseases.—The Board of Trustees of the American Foundation for Allergic Diseases announces the availability of three fellowships in research and clinical allergy for a period of two years each, carrying a stipend of $4500 for the first year, $4750 for the second, and a total of $750 for laboratory and travel expenses during the two-year period. The funds for these fellowships have been made available by Mr. John D. Rockefeller Jr. in a grant to the Foundation.

It is the hope of the Foundation that the recipients will be stimulated to enter the field of research in allergy and will be equipped to teach others. Unlike the usual procedure, the Foundation has established single fellowships with three investigators eminently qualified to teach the principles and techniques of scientific method in this field and in institutions where adequate clinical facilities exist. Applicants should apply directly to one of the following investigators, who will make the final selection: Dr. Frederick G. Germuth, Jr., Associate Professor of Pathology, The Johns Hopkins University Medical School, Baltimore (5); Dr. Colin M. MacLeod, Professor of Research Medicine, University of Pennsylvania, 820 Maloney Clinic, 36th and Spruce St., Philadelphia (4); Dr. Herman N. Eisen, Professor of Medicine (Dermatology), Washington University School of Medicine, Saint Louis.

Candidates must be graduates of approved medical schools and must have completed the graduate training required as a preliminary to certification by the Boards of Internal Medicine or Pediatrics; they are to divide their time between research and clinical training, and in the second year 10% or 15% of a candidate's time might be devoted to teaching. The respective institutions are undertaking to have this training credited toward the Subspecialty in Allergy by the Board of Internal Medicine and the Board of Pediatrics.

Applications should be received by May 10, 1957. Notification of the action taken on these applications will be sent to the candidate by June 10 of this year.

University of California Postgraduate Course in Pediatrics.—University of California Medical Extension will present a four-day postgraduate course in pediatrics, beginning June 11, at the University Medical Center in San Francisco. The program is being planned to cover endocrinology and related problems in the practice of pediatrics.

Dr. Lawson Wilkins, one of the foremost child endocrinologists in the country, will be guest lecturer. Dr. Wilkins is associate professor of pediatrics and director of the endocrinology section at The Johns Hopkins University School of Medicine. Program chairman will be Dr. George H. Schade, associate professor of pediatrics at the University of California Medical Center.

Further information may be obtained by applying to Seymour M. Farber, M.D., Head, Medical Extension, University of California Medical Center, San Francisco (22).

Fellowship in Pediatric Cardiology.—A Fellowship in Pediatric Cardiology is being offered at the John Gaston Hospital and the Division of Pediatrics of the University of Tennessee, Memphis. The position is available for a period of one year starting July 1, 1957, and carries a stipend of $3600 per annum. Candidates should have a minimum of a one-year pediatric residency or its equivalent.

Requests for application may be made by writing to Dr. F. Tom Mitchell, Professor of Pediatrics, University of Tennessee, College of Medicine, Memphis.

GENERAL NEWS

Grant for Study of Twins.—An unrestricted grant of $10,000 has been made to the Department of Pediatrics of the University of Louisville by the Courier-Journal and Louisville Times Foundation. The grant is to be used by Dr. Frank Falkner in a study of identical twins as part of the work of the department's Child Development Unit.

WHO Report on Administration of Maternal and Child Health Services.—In its second report (Administration of Maternal and Child Health Services: Second Report of the Expert Committee on Maternal and Child Health, World Health Organization, Technical Report Series, No. 115, 1957; price, $0.30) the WHO Expert Committee on Maternal and Child Health (MCH) emphasizes the need for sound administration and directs attention to current thought on the following subjects: content of a comprehensive MCH program, integration of MCH activities into the general public health and medical services, principles of program planning, the organization and structure of MCH services, techniques of administration, functions and preparation of physicians in MCH programs, the role of evaluation, and problems needing further research.

In conclusion, the Expert Committee recommends the holding of regional and national congresses as the best means to expedite the application of the principles of MCH administration elaborated in this report.

The report is available in English, Spanish, and French through local booksellers or from the Sales Section, Palais des Nations, Geneva, Switzerland. In the U. S. A. the central agent is the Columbia University Press, International Documents Service, *2960* Broadway, New York *27*.

Excerpta Medica Lifts the Curtain on Soviet Medicine.—As a result of plans initiated by the Public Health Service, National Institutes of Health, U. S. Department of Health, Education, and Welfare, arrangements have recently been completed with the Excerpta Medica Foundation whereby, for the first time in the history of medicine, an extensive review of the Soviet medical literature in all areas of medicine will now be available to medical science in the United States.

The plan calls for the translation and publication of abstracts of the Soviet medical literature, including reports of the work now being done in various cities throughout the U. S. S. R. The abstracts will be prepared by Soviet specialists most qualified to undertake this work, the material being edited and supervised by Excerpta Medica's own specialist permanent Editorial Committee of thirty Soviet scientists appointed by the Excerpta Medica Foundation in cooperation with the Presidium of the Academy of Medical Sciences of the U. S. S. R. These abstracts will be supplemented by verbatim translations of abstracts of the Soviet literature in specially selected fields.

The abstracts will be published under the title "Abstracts of Soviet Medicine" and will appear throughout 1957 as two separate publications: Part A, "Basic Medical Sciences," and Part B, "Clinical Medicine," totalling together some 1300 to 1400 pages.

The West has long realized that the inaccessibility of so much of the Soviet medical literature has left a great and perhaps vital gap in our knowledge. The primary objective of this far-reaching project is to assist in the creation of the final essential link in the interchange of medical information on a truly global basis.

Specialists Certified by the American Board of Pediatrics, Inc.—The following physicians were certified as specialists by the American Board of Pediatrics, Inc., in New Orleans, Feb. *22*, *23*, and *24*, 1957.

Bakshandeh, Ata, Elmhurst, L. I., N. Y.
Braverman, Irvin B., Chicago
Caldwell, James William, McAllen, Texas
Calma, Victor C., Galveston, Texas
Carrasco, Enrico Dederick, Fort Knox, Ky.
Clark, Robert L., Flint, Mich.
Cullen, Bernard, Leesville, La.
Damron, Joseph McDonald, Winchester, Va.
Davis, Sarah Fredericka, Birmingham, Ala.
Dempsey, Edwin B., Andrews, Texas
Donaldson, Edward Earl, Columbus
Dorman, Fred Iverson, Jr., Lakeland, Fla.
Doyle, Frances Ingell, Georgetown, S. C.
Erlanson, Andrew Cornell, St. Paul
Frank, Donald Joseph, Cincinnati
Frankel, Richard A., Houston, Texas
Greenman, Marshall Bernard, Richmond Heights, Mo.
Hall, Irving Edward, Jr., Bradenton, Fla.
Harris, Leonard, New York
Hidalgo, Hector Osvaldo, Santurce, P. R.
Hill, James Kirtley, Muskegon, Mich.
Howard, William K., Nashville, Tenn.
Hunt, Ann, Little Rock, Ark.
Klaus, Marshall H., Novato, Calif.
Lawson, Wilbur Glenn, Shattuck, Okla.
Lewis, James Willard, Chicago
Logsdon, George Richard, Pittsburgh
Lorenzen, Evelyn June, Houston, Texas
Lovin, Bailey J., Jr., Los Angeles
McCain, James Robert, Jacksonville, Fla.
McCurdy, Robert Seidel, Boulder, Colo.

MacNamee, Duncan Hugh, Marion, Ind.
Mannschreck, William C., Lewiston, Idaho
Marder, Gerard, Gastonia, N. C.
Mason, Brown Crosby, New Orleans
Matthews, Sanford John, Atlanta, Ga.
Moore, John Clifton, Jr., Lakeland, Fla.
Mulholland, William Melville, Minneapolis
Newton, William Allen, Jr., Columbus, Ohio
Nicholls, William W., Flint, Mich.
Novick, Rosalind, New Orleans
Nyhus, Ralph E., Rochester, Minn.
O'Hora, Bernard Anthony, Midland, Mich.
Penick, Roland Wingate, Greenville, S. C.
Peterson, Clifton Robert, New York
Phillips, Doris Sturgis, Birmingham, Ala.
Pomeranz, Virginia E., New York
Price, Morris A., Jacksonville, Fla.
Reilly, James Joseph, Pittsburgh
Sauers, Adelaide E., Columbus, Ohio
Schwartz, Mervin Herbert, El Paso, Texas
Shriner, John Franklin, Mobile, Ala.
Siegel, Robert M., Dallas, Texas
Venters, Homer D., Jr., Chattanooga, Tenn.
Wilber, John Vernon, Warren, Ohio
Wilder, Walter Llewellyn, Minneapolis
Wiley, Thomas M., Jr., Fort Myers, Fla.
Young, John B., Houston, Texas
Yow, Martha Dukes, Houston, Texas

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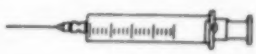

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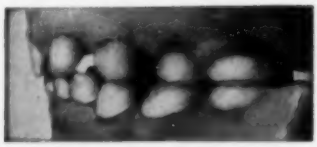

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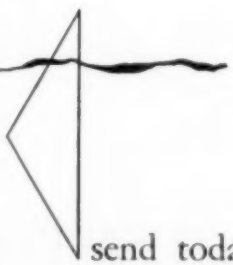

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Shwachman, H., The Child in Health and Disease, Grulee and Eley, 2nd Edit.

Shwachman, H. and Leubner, H., Advances in Pediatrics, VII, 249, 1955.

Kagan, B. M., Illinois Medical Journal, 107, 120, 1955.

Kumar, B. B., and Gibbs, G. E. A.M.A. Journal Diseases of Children, 91:606, 1956.

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1. Martin, E.A.: Roberts' Nutrition Work with Children, Chicago, University of Chicago Press, 1954, p. 53.
2. Sebrell, W.H.: Developing Modern Nutrition Programs, Public Health Reports, United States Department of Health, Education and Welfare 69:277 (Mar.) 1954.
3. Joint Report of the Council on Dental Health and the Council on Dental Therapeutics of the American Dental Association: Sugar and Dental Caries: The Effect on the Teeth of Sweetened Beverages and Other Sugar-Containing Substances, J. Am. Dent. A. 47:587 (Oct.) 1953.

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